AHRQ Healthcare Horizon Scanning System – Potential High-Impact Interventions Report

Priority Area 03: Cardiovascular Disease

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Statement of Funding and Purpose

This report incorporates data collected during implementation of the Agency for Healthcare Research and Quality (AHRQ) Healthcare Horizon Scanning System by ECRI Institute under contract to AHRQ, Rockville, MD (Contract No. HHSA290201000006C). The findings and conclusions in this document are those of the authors, who are responsible for its content, and do not necessarily represent the views of AHRQ. No statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

This report's content should not be construed as either endorsements or rejections of specific interventions. As topics are entered into the System, individual topic profiles are developed for technologies and programs that appear to be close to diffusion into practice in the United States. Those reports are sent to various experts with clinical, health systems, health administration, and/or research backgrounds for comment and opinions about potential for impact. The comments and opinions received are then considered and synthesized by ECRI Institute to identify interventions that experts deemed, through the comment process, to have potential for high impact. Please see the methods section for more details about this process. This report is produced twice annually and topics included may change depending on expert comments received on interventions issued for comment during the preceding 6 months.

A representative from AHRQ served as a Contracting Officer's Technical Representative and provided input during the implementation of the horizon scanning system. AHRQ did not directly participate in horizon scanning, assessing the leads for topics, or providing opinions regarding potential impact of interventions.

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None of the individuals compiling this information has any affiliations or financial involvement that conflicts with the material presented in this report.

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Preface

The purpose of the AHRQ Healthcare Horizon Scanning System is to conduct horizon scanning of emerging health care technologies and innovations to better inform patient-centered outcomes research investments at AHRQ through the Effective Health Care Program. The Healthcare Horizon Scanning System provides AHRQ a systematic process to identify and monitor emerging technologies and innovations in health care and to create an inventory of interventions that have the highest potential for impact on clinical care, the health care system, patient outcomes, and costs. It will also be a tool for the public to identify and find information on new health care technologies and interventions. Any investigator or funder of research will be able to use the AHRQ Healthcare Horizon Scanning System to select potential topics for research.

The health care technologies and innovations of interest for horizon scanning are those that have yet to diffuse into or become part of established health care practice. These health care interventions are still in the early stages of development or adoption, except in the case of new applications of already-diffused technologies. Consistent with the definitions of health care interventions provided by the Institute of Medicine and the Federal Coordinating Council for Comparative Effectiveness Research, AHRQ is interested in innovations in drugs and biologics, medical devices, screening and diagnostic tests, procedures, services and programs, and care delivery.

Horizon scanning involves two processes. The first is identifying and monitoring new and evolving health care interventions that are purported to or may hold potential to diagnose, treat, or otherwise manage a particular condition or to improve care delivery for a variety of conditions. The second is analyzing the relevant health care context in which these new and evolving interventions exist to understand their potential impact on clinical care, the health care system, patient outcomes, and costs. It is NOT the goal of the AHRQ Healthcare Horizon Scanning System to make predictions on the future use and costs of any health care technology. Rather, the reports will help to inform and guide the planning and prioritization of research resources.

We welcome comments on this Potential High-Impact Interventions report. Send comments by mail to the Task Order Officer named in this report to: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to: effectivehealthcare@ahrq.hhs.gov.

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Background

Horizon scanning is an activity undertaken to identify technological and system innovations that could have important impacts or bring about paradigm shifts. In the health care sector, horizon scanning pertains to identification of new (and new uses of existing) pharmaceuticals, medical devices, diagnostic tests and procedures, therapeutic interventions, rehabilitative interventions, behavioral health interventions, and public health and health promotion activities. In early 2010, the Agency for Healthcare Research and Quality (AHRQ) identified the need to establish a national Healthcare Horizon Scanning System to generate information to inform comparative-effectiveness research investments by AHRQ and other interested entities. AHRQ makes those investments in 14 priority areas. For purposes of horizon scanning, AHRQ's interests are broad and encompass drugs, devices, procedures, treatments, screening and diagnostics, therapeutics, surgery, programs, and care delivery innovations that address unmet needs. Thus, we refer to topics identified and tracked in the AHRQ Healthcare Horizon Scanning System generically as "interventions." The AHRQ Healthcare Horizon Scanning System implementation of a systematic horizon scanning protocol (developed between September 1 and November 30, 2010) began on December 1, 2010. The system is intended to identify interventions that purport to address an unmet need and are up to 3 years out on the horizon and then to follow them up to 2 years after initial entry into the health care system. Since that implementation, review of more than 16,200 leads about potential topics has resulted in identification and tracking of about 1,900 topics across the 14 AHRQ priority areas and 1 cross-cutting area; about 500 topics are being actively tracked in the system.

Methods

As part of the Healthcare Horizon Scanning System activity, a report on interventions deemed as having potential for high impact on some aspect of health care or the health care system (e.g., patient outcomes, utilization, infrastructure, costs) is aggregated twice a year. Topics eligible for inclusion are those interventions expected to be within 0–3 years of potential diffusion (e.g., in phase III trials or for which some preliminary efficacy data in the target population are available) in the United States or that have just begun diffusing and that have completed an expert feedback loop.

The determination of impact is made using a systematic process that involves compiling information on topics and issuing topic drafts to a small group of various experts (selected topic by topic) to gather their opinions and impressions about potential impact. Those impressions are used to determine potential impact. Information is compiled for expert comment on topics at a granular level (i.e., similar drugs in the same class are read separately), and then topics in the same class of a device, drug, or biologic are aggregated for discussion and impact assessment at a class level for this report. The process uses a topic-specific structured form with text boxes for comments and a scoring system (1 minimal to 4 high) for potential impact in seven parameters. Participants are required to respond to all parameters.

The scores and opinions are then synthesized to discern those topics deemed by experts to have potential for high impact in one or more of the parameters. Experts are drawn from an expanding database ECRI Institute maintains of approximately 350 experts nationwide who were invited and agreed to participate. The experts comprise a range of generalists and specialists in the health care sector whose experience reflects clinical practice, clinical research, health care delivery, health business, health technology assessment, or health facility administration perspectives. Each expert uses the structured form to also disclose any potential intellectual or financial conflicts of interest

(COIs). Perspectives of an expert with a COI are balanced by perspectives of experts without COIs. No more than two experts with a possible COI are considered out of a total of the seven or eight experts who are sought to provide comment for each topic. Experts are identified in the system by the perspective they bring (e.g., clinical, research, health systems, health business, health administration, health policy).

The topics included in this report had scores *and/or* supporting rationales at or above the overall average for all topics in this priority area that received comments by experts. Of key importance is that topic scores alone are not the sole criterion for inclusion—experts' rationales are the main drivers for the designation of potentially high impact. We then associated topics that emerged as having potentially high impact with a further subcategorization of "lower," "moderate," or "higher" within the high-impact-potential range. As the Healthcare Horizon Scanning System grows in number of topics on which expert opinions are received and as the development status of the interventions changes, the list of topics designated as having potentially high impact is expected to change over time. This report is being generated twice a year.

For additional details on methods, please refer to the full AHRQ Healthcare Horizon Scanning System Protocol and Operations Manual published on AHRQ's Effective Health Care Web site.

Results

The table below lists the nine topics for which (1) preliminary phase III data for drugs, phase II (or equivalent) data for devices and procedures, or some human data for off-label uses or programs were available; (2) information was compiled and sent for expert comment before October 27, 2013, in this priority area; *and* (3) we received six to eight sets of comments from experts between April 9, 2012, and October 29, 2013. (Forty-three topics were being tracked in this priority area as of October 29, 2013.) We present six summaries on six topics (indicated below by an asterisk) that emerged as having potential for high impact on the basis of experts' comments. The material on interventions in this Executive Summary and report is organized alphabetically by disease state and then by interventions within that disease state. Readers are encouraged to read the detailed information on each intervention that follows the Executive Summary.

Priority Area 03: Cardiovascular

Topic	High-Impact Potential
1. * Catheter-based renal denervation (Symplicity System) for treatment-resistant hypertension	Moderately high
2. Imatinib (Gleevec) for treatment of pulmonary artery hypertension	No high-impact potential at this time
3. Implantable cardiac monitor (AngelMed Guardian System) for detecting myocardial infarction	No high-impact potential at this time
4. * Lomitapide (Juxtapid) for treatment of homozygous familial hypercholesterolemia	Moderately high
5. * Portable Freedom Driver for in-home support of the Total Artificial Heart	Lower end of the high-impact-potential range
6. Recombinant human relaxin-2 (serelaxin) for treatment of acute heart failure	No high-impact potential at this time
7. * Subcutaneous Implantable Cardioverter-Defibrillator (S-ICD) for treatment of life-threatening ventricular tachyarrhythmias	Lower end of the high-impact-potential range
8. * Transcatheter aortic valve implantation (CoreValve) for treatment of severe aortic stenosis	High
9. * Transcatheter mitral valve repair (MitraClip) for treatment of mitral regurgitation	High

Discussion

Research activity in all disease areas of the cardiovascular priority area is robust and addresses both novel and incremental innovations that could affect patient outcomes, shift care models, and affect costs and care delivery. Most of the innovations being tracked, as well as the innovations deemed by expert comments to have potential for high impact pertain to cardiovascular devices that provide support for end-stage heart failure or address valve problems, arrhythmias, and treatment-resistant hypertension. Only one pharmaceutical, lomitapide, was deemed as having potential for high impact; another one, relaxin, has garnered widespread attention in some circles, but experts commenting on this topic wanted to see more data before attributing it with potential for high impact.

Arrhythmia

According to the American Heart Association (AHA), arrhythmias (abnormal heartbeats) are a major source of cardiovascular-related morbidity and mortality. Ventricular tachycardia (rapid heartbeat) and ventricular fibrillation (unsynchronized heartbeat) reduce the heart's pumping ability and can cause collapse, cardiac arrest, and sudden death. These conditions are believed to contribute to the more than 400,000 deaths from sudden cardiac arrest that occur in the United States each year. Numerous drugs and implantable devices exist to treat arrhythmia. Unfortunately, drugs for rhythm and rate control carry significant risks of adverse events, and available implantable devices often contraindicate certain procedures (e.g., magnetic resonance imaging [MRI]). Therefore, a significant unmet need exists for better and safer treatments for patients with forms of cardiac arrhythmia. Experts commented on one intervention with potential high impact in treating arrhythmia.

Subcutaneous Implantable Cardioverter-Defibrillator (S-ICD) for Treatment of Life-Threatening Ventricular Tachyarrhythmias

- **Key Facts:** Before the Subcutaneous Implantable Cardioverter-Defibrillator (S-ICD®) System (Boston Scientific Corp., Natick, MA) was approved for marketing, only implantable cardioverter-defibrillators (ICDs) with implanted leads were available. ICDs used to prevent sudden cardiac death by treating ventricular tachyarrhythmias required implanting a transvenous lead in the heart. Complications that arise from ICD implantation are often related to lead-implantation and lead failure over time, and procedures to remove these faulty leads are often associated with morbidity and mortality. The S-ICD is intended to be a minimally invasive device that does not require electrode lead placement in or on the heart. Further, the device does not require imaging equipment for placement because the system components are designed to be positioned using only anatomic landmarks. The U.S. Food and Drug Administration (FDA) approved the S-ICD in September 2012. According to FDA, the device is approved for use only in patients who do not require a pacemaker or pacing therapy.

  In February 2013, Jarman and colleagues reported on clinical experience using the S-ICD in the United Kingdom. Investigators surveyed all UK hospitals implanting the S-ICD; 76% (19 of 25) of hospitals responded with data on 111 patients. Patients had a median age of 33 years (range 10–87 years). Underlying pathologies included primary electrical disease, 43%; hypertrophic cardiomyopathy, 20%; ischemic cardiomyopathy, 14%; congenital heart disease, 12%; idiopathic dilated cardiomyopathy, 5%; and other cardiomyopathies, 6%. Overall, 17% of patients (19 of 111) required 20 repeat operations related to S-ICD

placement; this included 10 of 111 (9%) patients in whom the device was permanently removed. During the study period, S-ICDs delivered 24 appropriate shocks in 13 patients and 51 inappropriate shocks in 17 patients. Investigators found no instances of the device failing to detect or treat (defibrillate) ventricular arrhythmias above the programmed detection rate. Among the 51 inappropriate shocks, 41 were due to T-wave over-sensing.

In April 2013, a report in Medical Device and Diagnostic Industry stated that demand for the S-ICD was outstripping supply, and a company spokesperson was quoted as saying the supply would remain limited until the next generation of the device was launched in late 2013. In coverage policies addressing conventional ICDs, several private, third-party payers described the S-ICD as investigational or experimental and, therefore, denied coverage for the technology, even after the technology received FDA approval. Some payers noted a desire for more data to show safety and efficacy that is equivalent to transvenous ICDs. The American Medical Association Current Procedural Terminology has established category III codes for the S-ICD to enable tracking of use. The U.S. Centers for Medicare & Medicaid Services (CMS) has a national coverage determination for ICDs and criteria for coverage, but does not specifically mention the S-ICD system. The cost of the device is reported to be similar to that of conventional ICDs; however, the procedure purportedly takes less time to perform because it can be performed in an outpatient setting with no need for fluoroscopy, other imaging, or an electrophysiology laboratory.

- **Key Expert Comments:** Experts were optimistic that this intervention has some potential to improve patient health outcomes by reducing complications associated with lead-based ICDs and associated secondary surgeries that carry a high risk of morbidity and some mortality. This optimism was diluted partially by a couple of experts who suggested that this device's limited pacing capabilities would temper widespread diffusion and impact. Because the implantation procedure requires fewer resources and can be performed in an outpatient setting, this intervention could shift care delivery to a less-invasive setting and result in shorter hospital stays than for conventional ICD implantation and possibly lower costs associated with the procedure.
- **Potential for High Impact:** Lower end of the potential high-impact range

Genetic Disorder

Familial hypercholesterolemia (FH) is an inherited genetic disorder that causes accumulation of high levels of low-density lipoprotein (LDL) cholesterol (LDL-C) due to a defect on chromosome 19 that impairs the LDL receptor's ability to remove LDL from the bloodstream. According to the U.S. National Human Genome Research Institute, FH can cause premature onset of coronary artery disease, myocardial infarction, and cardiac-related death. FH is an autosomal dominant disorder, meaning a defect needs to be present on only one of two number 19 chromosomes for the person to be affected. Patients who have inherited only one defective LDL receptor gene are said to have heterozygous FH. In rare instances, the genetic defect is inherited from both parents, causing a genetic condition known as homozygous (Ho) FH, which exhibits increased severity compared with heterozygous FH. According to the Familial Hypercholesterolemia Foundation, heterozygous FH occurs in approximately 1 of every 500 persons and HoFH occurs in approximately 1 of every 1 million persons in the United States. Experts commented on one intervention with potential high impact in treating FH.

Lomitapide (Juxtapid) for Treatment of Homozygous Familial Hypercholesterolemia

- **Key Facts:** Lomitapide is a microsomal triglyceride transfer protein inhibitor that is indicated as a daily oral therapy for treating HoFH. In December 2012, FDA approved lomitapide (Juxtapid™) for marketing. In the trial that served as the basis for the approval, investigators reported that lomitapide at a median dose of 40 mg per day reduced LDL-C concentrations by a mean of 50% at 26 weeks from baseline. By week 56, LDL-C concentrations were reduced by 44% (95% confidence interval [CI], -57 to -31; $p<0.0001$). At week 78, LDL-C concentrations were reduced by 38% (-52 to -24; $p<0.0001$). The most commonly reported adverse events were gastrointestinal symptoms. Four patients had aminotransaminase levels measured at more than five times the upper limit of normal; the increase resolved after dose reduction or temporary halt of lomitapide therapy. No patient permanently stopped lomitapide because of liver abnormalities. Retail prices for a 28-day lomitapide supply range from more than $25,000 for 5 mg tablets to more than $27,000 for 20 mg tablets (as of November 2013) with the use of a coupon. Representative, private, third-party payers that include lomitapide in their drug formularies typically have precertification and step-therapy policies in place that govern coverage of the drug. These payers generally place quantity limits on the drug and require annual recertification and documentation of patients' positive clinical response from lomitapide before extending coverage to renewed prescriptions for the drug. With regard to diffusion, the company reports of the drug's sale through the third quarter of 2013 have exceeded investor analyst and industry projections by about 25%. The company indicated that new prescription rates were accelerating and patient discontinuation of therapy was less than 10% in the first half of 2013; medication adherence rates were stated to be 80% to 90%.
- **Key Expert Comments:** Experts generally agreed that lomitapide has a moderate to high potential to fill the unmet need for effective treatment for HoFH, given that it may serve as a bridge between conventional lipid-lowering drugs, such as statins, and invasive treatments, such as apheresis, which is costly, labor-intensive, and may not be readily accessible to all patients with this rare condition. Experts agreed that lomitapide would likely be adopted widely by physicians for the targeted population of patients with HoFH. The experts also thought that a majority of patients would likely accept lomitapide as long as out-of-pocket costs for lomitapide therapy were not prohibitive.
- **Potential for High Impact:** Moderate

Heart Failure

Heart failure adversely affects quality of life as well as life expectancy and can develop from any condition that overloads, damages, or reduces the heart muscle efficiency, impairing the ventricles' ability to fill with or eject blood. According to AHA, about 5.7 million U.S. adults aged 20 years or older were living with heart failure in 2009. Those surviving a heart attack are most at risk. AHA estimates that for the U.S. population 65 years of age or older, heart failure incidence is about 10 per 1,000 people. Nearly 550,000 new cases of heart failure occur each year. In 2005 (the most recent year for which mortality statistics are available), more than 292,000 patients died in the United States with a prior diagnosis of heart failure; it was listed as the underlying cause in nearly 59,000 deaths and a contributing (secondary) factor in the remaining cases. Heart failure prevalence has increased during the past 20 years, and the number of patients who progress to end-stage heart failure is expected to grow because of increased survival in patients with coronary artery disease, an increased population of aging patients, and significant advances in the control of other potentially

lethal diseases. Because of the clear unmet need for effective therapies for heart failure and its underlying cause, many new drugs, biologics, and devices are under study for treating patients with heart failure. Experts thought one intervention had potential high impact for treating heart failure.

Portable Freedom Driver for In-Home Support of the Total Artificial Heart

- **Key Facts:** The Freedom® Driver System, made by SynCardia Systems, Inc., of Tucson, AZ, is a wearable, pneumatic, portable driver under development to enable at-home support for the company's temporary Total Artificial Heart (TAH-t) in patients awaiting a heart transplant. The TAH-t, approved as a bridge to transplantation by FDA in October 2004, is indicated for use in cardiac transplant–eligible patients at risk of imminent death from nonreversible biventricular failure. The TAH-t is traditionally powered by a conventional pneumatic driver system, which is a large and cumbersome device that requires patients to remain hospitalized while awaiting a donor heart. A portable driver system that might allow patients to be discharged from the hospital while awaiting a suitable donor heart would address a significant unmet need for the relatively small number of people in this patient population. The battery-powered Freedom Driver System weighs 13.5 lb and is carried by the patient in a backpack or shoulder bag. As with conventional, large, hospital-based pneumatic driver systems, the Freedom driver is connected to the implantable TAH-t by a flexible pneumatic driveline that passes through the patient's skin in the left chest just below the ribs. The driver flashes a light or sounds an alarm when the system requires the user's attention. A clinical trial of the driver is ongoing. As of November 2012 (the latest company update), the company had reported that 41 of 55 patients supported with the Freedom driver in an investigational device exemption (IDE) clinical trial in the United States had been discharged from the hospital using the portable driver.
- **Key Expert Comments:** Although this intervention is expected to have a significant impact on quality of life for patients with a TAH-t and may reduce health care costs associated with lengthy hospital stays, the patient population for which this device is intended is small, which tempers its overall potential impact on the health care system. However, experts thought that shifting care from the inpatient to the outpatient setting would be a very important effect of this intervention, if approved for marketing.
- **Potential for High Impact:** Lower end of the high-impact-potential range

Hypertension

Hypertension, or high blood pressure, affects about one-third of the adult population in the United States and has long been described as the "silent killer" because it often shows no specific symptoms. However, more pronounced symptoms are associated with complications of severe or long-term hypertension and include severe headache, dizziness or confusion, nausea, fatigue, blurred vision, chest pain, difficulty breathing, irregular heartbeat, and blood in the urine. According to AHA, about 76.4 million people in the United States have hypertension. National health surveys from both highly industrialized and developing nations suggest that hypertension is effectively managed in only 11.2% of cases. Hypertension was the primary cause of 61,762 deaths in the United States in 2009, the most recent year for which statistics are available, according to AHA and the American Stroke Association. Experts commented on one intervention with potential for high impact in treating hypertension.

Catheter-Based Radiofrequency Ablation (Symplicity System) Renal Denervation for Treatment-Resistant Hypertension

- **Key Facts:** Lowering high blood pressure has been associated with significantly lower rates of stroke, heart attack, and heart failure. However, inadequately controlled hypertension remains a problem for a growing number of people. The Symplicity™ Catheter System (Medtronic, Inc., Minneapolis, MN) is in development for treatment-refractory hypertension. The device is intended to enable a physician to apply radiofrequency energy to ablate renal nerves from within the renal artery without adversely affecting other nerves in the abdomen, pelvis, or lower extremities. In clinical trials, the minimally invasive procedure has taken about 40 minutes to perform. In March 2013, investigators reported 24-month results from Symplicity HTN-2, the first randomized trial investigating renal denervation. Among 40 patients who received Symplicity renal denervation, blood pressure at 24 months dropped by 29/10 mm Hg from 178/97 mm Hg at baseline ($p<0.01$). Among 26 control-group patients who crossed over to receive renal denervation after 6-month primary endpoint assessment (crossover group), average blood pressure at 24 months dropped by 35/13 mm Hg from 178/98 mm Hg at baseline ($p<0.01$). Further, investigators observed no device-related serious adverse events, no late vascular complications, and no significant declines in kidney function compared with baseline values through 24 months. According to the company, physicians perform the procedure in a catheterization laboratory using standard interventional techniques similar to those used for renal stent implantation. In May 2013, Medtronic completed patient enrollment in the Symplicity HTN-3 trial, a phase III randomized controlled trial intended to support a U.S. marketing approval application. The company also announced that the Symplicity device would be one of the first medical devices evaluated under the FDA-CMS parallel review program, which enables CMS to begin a national coverage determination while FDA completes its safety and efficacy review.
- **Key Expert Comments:** Experts commenting on this intervention agreed that it has the potential to fill an important gap in treating refractory hypertension and would likely be accepted by clinicians and patients. However, this intervention's potential impact is tempered by its lack of long-term outcomes data and the fact that although it can be easily accommodated in a catheterization laboratory, it introduces a surgical procedure into a treatment paradigm that previously was limited to medical management. Thus, it could shift care from medical management to a procedure and increase demand on catheterization laboratory infrastructure.
- **Potential for High Impact:** Moderate

Valve and Structural Disorders

This section includes topics that purport to address unmet needs for certain disorders of heart valves.

Aortic valve stenosis: This condition affects primarily the elderly and obstructs normal blood flow through the aortic valve, the most likely of the heart's four valves to fail because of disease. Severe, untreated aortic valve stenosis can eventually lead to heart failure or sudden cardiac arrest. According to researchers, in the United States, about 29% of people aged 65 years or older and 37% of people aged 75 years or older have aortic sclerosis, a precursor condition to aortic stenosis characterized by mild thickening or calcification of the aortic valve without restricted leaflet motion. About 1% to 2% of the population is living with a bicuspid aortic valve, a congenital defect in which the aortic valve develops two instead of three normal valve leaflets. According to Novaro (2011), half of this population will develop aortic stenosis. Experts commented on one intervention with potential for high impact in treating aortic valve stenosis.

Transcatheter Aortic Valve Implantation (CoreValve) for Treatment of Severe Aortic Stenosis

- **Key Facts:** New, minimally invasive approaches are making the therapeutic benefit of aortic valve replacement an option for patients with severe aortic stenosis who are not candidates for open-heart valve surgery or who are at high risk of complications from open-heart surgery. One system (CoreValve®) is approved only for investigational use in the United States. The CoreValve System (Medtronic) features a porcine pericardial tissue valve mounted in a self-expanding, hourglass-shaped, nitinol-alloy mesh frame. The bioprosthetic valve is deployed using an 18-French diameter delivery catheter with a set of disposable catheter-loading components in a procedure that lasts up to 4 hours and requires, on average, a 3- to 5-day hospital stay. Medtronic received an IDE designation for its CoreValve trial from FDA in October 2010, and trials are under way.
  In May 2012, CMS released a national coverage determination stating that CMS "covers transcatheter aortic valve replacement (TAVR) under Coverage with Evidence Development (CED)" when the procedure is used for "the treatment of symptomatic aortic valve stenosis when furnished according to an FDA approved indication" and when numerous conditions are met, including the required credentials and experience of the facilities and surgeons who perform the procedure.
- **Key Expert Comments:** Experts commenting on this intervention agreed that it would offer an important and effective new treatment modality for patients who have no other effective medical options and are not candidates for open surgery. Experts thought that this intervention would improve patient health outcomes and that an increase in patient volume would occur as this intervention diffuses. Expert opinions diverged about whether and how much this intervention would disrupt health care infrastructure, but they agreed that the intervention has the potential to both increase (in the short term) and decrease (in the long term) health care costs associated with this patient population.
- **Potential for High Impact**: High

Mitral regurgitation (MR): MR is defined broadly as a backward flow of blood from the heart's left ventricle into the left atrium during contraction. MR can be divided into two major categories: primary, or organic MR, and secondary, or functional MR (FMR). FMR is associated with poor long-term survival, and its presence in patients with ischemic and dilated cardiomyopathy is an independent risk factor for cardiovascular morbidity and mortality. According to Mayo Clinic

investigators, without treatment, severe MR can lead to congestive heart failure or potentially life-threatening cardiac arrhythmias. Significant MR occurs in an estimated 1% to 2% (about 4 million) of the U.S. population. More than 250,000 cases of significant MR are diagnosed each year in the United States and about 50,000 people undergo some type of surgery for the disease, according to one manufacturer in the field. Experts commented on one intervention with potential high impact in treating MR.

Transcatheter Mitral Valve Repair (MitraClip) for Treatment of Mitral Regurgitation

- **Key Facts:** Transcatheter mitral valve repair with the MitraClip® device (Abbott Laboratories, Abbott Park, IL) is intended to simulate the functional effects achieved by the standard open-surgery repair procedure used for treating MR. In the standard procedure, a surgeon sutures together the edges of the two opposing mitral valve leaflets at the center of the valve opening, leaving two smaller openings on either side that close more completely than a single large opening. In a MitraClip procedure, the physician uses a transcatheter approach in which a two-armed, flexible metal clip covered in polyester fabric is used, rather than the sutures used during open surgery. In 2013, investigators reported 1-year outcomes from 59 patients with severe, symptomatic MR and reduced ejection fraction who received MitraClip. Procedural efficacy was measured by the reduction in MR and improvement in New York Heart Association (NYHA) functional classification. Investigators reported that device implantation was associated with reduced MR and improved NYHA functional class, translating into improved 6-minute walk test distance. Followup echocardiography suggested a reversal in heart enlargement, with reduced left atrial volume and left ventricular end-systolic diameter and increased left ventricular ejection fraction (LVEF). These results were consistent with outcomes of a subgroup of 25 patients with severely reduced LVEF (23±2%), suggesting that sicker patients also reaped a benefit from MitraClip. Investigators reported 30-day mortality of 2.9%. Also in 2013, investigators reported outcomes from 117 patients in the GRASP Registry. Investigators reported acute procedural success in all patients and no procedure-related mortality. Outside the United States, the manufacturer issued a product recall in 2011 and a safety advisory in early 2013. Both issues were related to potential problems with the MitraClip delivery system that could malfunction and require emergency open-heart surgery to correct. MitraClip received the Conformité Européene (CE) mark for marketing in Europe in 2008 for use as a nonsurgical option in patients with severe MR. In October 2013, FDA granted marketing approval for the MitraClip delivery system for treating significant symptomatic degenerative mitral regurgitation.
- **Key Expert Comments:** Overall, experts commenting on this technology agreed this procedure addresses a considerable unmet need and has the potential to improve patient health, although some experts thought more data concerning safety and long-term outcomes are needed. Experts were split on whether this technology would disrupt health care delivery. Some experts believe that little disruption to health care delivery would occur because the infrastructure is already in place, while other experts believe that the increase in case volume might cause a large disruption to health care delivery. The majority of experts believe the MitraClip would increase health care costs, but more long-term data are needed to determine whether it could decrease long-term costs by reducing the need for standard therapy for this population.
- **Potential for High Impact:** High

Arrhythmia Intervention

Subcutaneous Implantable Cardioverter-Defibrillator (S-ICD) for Treatment of Life-Threatening Ventricular Tachyarrhythmias

Unmet need: Implantable cardioverter-defibrillators (ICDs) are an established therapy to prevent sudden cardiac arrest from ventricular arrhythmias. Conventional ICDs have a transvenous lead that is placed in the heart for cardiac sensing and defibrillation.[1] This transvenous lead, however, can cause serious complications, both during and after implantation. Complications such as cardiac tamponade, pneumothorax, and hemothorax can occur during the lead implantation, and lead failure can occur after implantation, which is a major limitation of this therapy.[1] Lead failure can generate unnecessary shocks or fail to provide necessary shocks, and removing faulty leads is often associated with significant morbidity and mortality. Lead problems have occurred in up to an estimated 40% of cases for some lead models. This has prompted development of an ICD system that replaces conventional transvenous leads with a single, subcutaneous lead in the chest.[1-3]

Intervention: The Subcutaneous Implantable Cardioverter-Defibrillator (S-ICD®) System is indicated "to provide defibrillation therapy for the treatment of life-threatening ventricular tachyarrhythmias in patients who do not have symptomatic bradycardia, incessant ventricular tachycardia, or spontaneous, frequently recurring ventricular tachycardia that is reliably terminated with anti-tachycardia pacing" (i.e., the device is approved only for patients who do not require a pacemaker or pacing therapy).[4,5] The S-ICD System components consist of the SQ-RX® pulse generator, the Q-Trak® subcutaneous electrode, the Q-Guide™ electrode insertion tool, and the Q-Tech™ programming system.[6] The battery-powered, computer-controlled pulse generator is intended to detect cardiac activity and provide defibrillation energy to the heart through the single subcutaneous electrode; the manufacturer states that the battery lasts 5.1 years.[6,7] The external programmer is designed to allow clinicians to set parameters for the pulse generator and retrieve data.[6]

According to the manufacturer, a physician typically implants the S-ICD during an outpatient procedure using anatomic landmarks rather than fluoroscopic imaging guidance to position the device.[7-9] To implant the device, a physician creates a pouch for the pulse generator beneath the skin under the left arm using an incision along the rib cage around the fifth and sixth intercostal spaces at the mid-axillary line.[7] Two small incisions to the left of the sternum are used to thread the subcutaneous electrode under the skin and connect it to the pulse generator.[7] Before closing the incisions, the physician tests and adjusts the system using the external programmer.[7,8]

Clinical trials: In February 2013, Jarman and colleagues reported on the early phase clinical experience using the S-ICD in the United Kingdom.[10] Investigators surveyed all UK hospitals implanting the S-ICD, of which 76% (19 of 25) of hospitals responded with data on 111 patients. Patients had a median age of 33 years (range 10–87 years). Underlying pathologies treated with the S-ICD included: primary electrical disease, 43%; hypertrophic cardiomyopathy, 20%; ischemic cardiomyopathy, 14%; congenital heart disease, 12%; idiopathic dilated cardiomyopathy, 5%; and other cardiomyopathies, 6%.[10] Overall, 17% of patients (19 of 111) required 20 repeat operations related to S-ICD placement, including 9% of patients (10 of 111) in whom the device was permanently removed.

During the study period, S-ICDs delivered 24 appropriate shocks, including 10 shocks for ventricular fibrillation, in 12% of patients (13 of 111). One patient died from a cardiac arrhythmia, but investigators found no instances of the device failing to detect or treat (defibrillate) ventricular arrhythmias above the programmed detection rate. Devices delivered 51 inappropriate shocks in 15% of patients (17 of 111). Among inappropriate shocks, 80% (41 of 51) were due to T-wave

over-sensing. Patients who received inappropriate shocks due to T-wave over-sensing were significantly younger than patients who did not (24±10 vs. 37±19 years; p=0.02).[10]

Manufacturer and regulatory status: Boston Scientific Corp., of Natick, MA, makes the S-ICD; Boston Scientific acquired the device's originator, Cameron Health, in 2012.[11] According to the company, the device has been commercially available in Europe and New Zealand since 2009.[8] In the United States, the U.S. Food and Drug Administration (FDA) approved the S-ICD in September 2012.[5] As part of the approval, FDA is requiring Boston Scientific to conduct a 5-year, 1,600-patient postmarket study to assess the device's long-term safety and performance and to assess differences in effectiveness across sexes.[5]

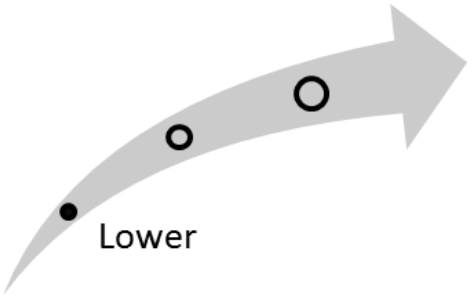
Diffusion: After FDA approval, Boston Scientific planned a phased launch of the system in the United States to ensure that clinicians were trained to use the system in a safe and effective way.[4] As of September 2012 (the latest figures reported), the company stated that more than 1,400 S-ICD systems had been implanted in patients around the world.[4] In April 2013, a report in Medical Device and Diagnostic Industry stated that demand was outstripping supply and a company spokesperson was quoted as saying the supply would remain limited until the next generation of the device was launched in late 2013.[12] The American Medical Association Current Procedural Terminology has established category III codes for the S-ICD to enable tracking of utilization.[13]

The device's cost is reported to be similar to costs of conventional transvenous-lead ICDs; however, the procedure may cost less than conventional ICD implantation because it can be performed in an outpatient setting with no need for fluoroscopy or an electrophysiology laboratory, taking less time.[9] The U.S. Centers for Medicare & Medicaid Services (CMS) national coverage determination on ICDs does not mention the S-ICD specifically, but ICDs that are FDA approved are covered as medically necessary when a beneficiary meets certain eligibility criteria.[14] In private, third-party payer coverage policies addressing ICDs (generally updated or revised after FDA approval of the S-ICD), several payers that publish their coverage policies online consider the S-ICD to be investigational or experimental and deny coverage, noting a desire for more data establishing safety and efficacy that is equivalent to transvenous ICDs. Among the payers that deny coverage at this time for the S-ICD are Aetna,[15] Anthem,[16] Blue Cross Blue Shield (BCBS) of Arizona,[17] BCBS of Kansas City,[18] BCBS of North Carolina,[19] CIGNA,[20] Empire BCBS,[21] Humana,[22] and United HealthCare.[23]

Clinical Pathway at Point of This Intervention

According to the American College of Cardiology (ACC) and the American Heart Association (AHA), prophylactic ICDs are the preferred treatment for patients with ventricular fibrillation who are at risk of sudden cardiac arrest. For patients who do not meet criteria for an ICD, beta blockers are considered first-line therapy, and radiofrequency (RF) ablation might be indicated. For patients with ventricular fibrillation refractory to ICD, drug therapy and RF catheter ablation or antiarrhythmic surgery might be warranted.[24] The S-ICD system competes directly with standard ICD systems that require a transvenous electrode in the heart. Clinicians might prefer the S-ICD System to other ICD systems because it offers the potential to reduce procedure-related complications and lead-related adverse events and does not require imaging during placement.

Figure 1. Overall high-impact potential: Subcutaneous Implantable Cardioverter-Defibrillator (S-ICD) for treatment of life-threatening ventricular tachyarrhythmias



Overall, experts commenting on this topic thought that this intervention might have some potential to improve patient health outcomes by reducing complications associated with lead-based ICDs and associated secondary surgeries that carry a high risk of morbidity and some mortality. Because the implantation procedure requires fewer resources and can be performed in an outpatient setting, this intervention could shift care delivery to a less-invasive setting and bring about shorter hospital stays. However, some experts suggested that this device's limited capabilities, compared with other ICDs, might temper its diffusion and impact on patient health outcomes. Based on this input, our overall assessment is that this intervention is in the lower end of the high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical, research, health systems, and health administration backgrounds, offered perspectives on this intervention.[25-30] One of these experts declared a potential conflict of interest (COI) because the expert is an electrophysiologist who acts as a consultant to original developer Cameron Health and was an investigator in the S-ICD investigational device exemption (IDE) study.[27] This potential COI is balanced by the perspectives of other experts who reported having no COIs. We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: The unmet need this intervention purportedly addresses is important and the intervention has potential to meet that need, the experts generally agreed, basing their opinions on both the "high incidence of lead failure in conventional ICDs and the high morbidity and mortality associated with lead failure and replacement in these devices," as one expert put it.[25] They generally thought that the S-ICD would improve patient outcomes, because of the soundness of the theory underlying the technology and also on the data collected thus far.

Acceptance and adoption: Both patients and clinicians would likely adopt this device if it shows good efficacy relative to existing ICDs, the experts agreed; however, a few experts suggested that longer-term data will be necessary before clinicians fully embrace the technology and thought that diffusion might be constrained by the device's limited pacing capabilities. One expert, speaking from a clinical perspective, stated: "The main advantage of the system is its degree of invasiveness, which is much less [than currently available ICDs]."[29] However, this expert stated that substantial weaknesses exist with a device that does not have a transvenous lead, does not have the ability to perform event tachycardia pacing or bradycardia pacing, and is large and placed in the axilla.[29]

Health care delivery infrastructure and patient management: Because ICD placements are common, this intervention is unlikely to significantly disrupt current care models or operational processes, with a few exceptions, experts noted. First, because the device does not use transvenous leads and can be placed using only anatomic landmarks, specialized cardiac procedure rooms and fluoroscopy or other imaging techniques might be used less, the experts commented. Second, experts commented,

the device can be implanted in an outpatient setting, which would shift care from the inpatient to outpatient setting. Finally, they noted that physicians implanting the device might require some initial S-ICD-specific training. Although the S-ICD's cost is similar to that of other ICD systems, experts thought that by avoiding lead complications and shifting the setting from inpatient to outpatient surgery, this intervention has the potential to reduce some financial burden.

Health disparities: All experts generally agreed that the S-ICD has minimal potential to affect health disparities among patients who might be candidates for ICD therapy. One expert with a research background suggested that the S-ICD might provide a therapeutic option for a subset of patients who are ineligible to receive a conventional transvenous-lead ICD and for whom medical therapy is not an option.[28]

Genetic Disorder Intervention

Lomitapide (Juxtapid) for Treatment of Homozygous Familial Hypercholesterolemia

Unmet need: Despite the availability of lipid-lowering pharmacotherapies, many patients with homozygous familial hypercholesterolemia (HoFH) do not achieve acceptable lipid levels and remain at increased risk of having early coronary events and sudden death.[31] Nonpharmacologic interventions, such as apheresis and liver transplantation, are costly, invasive, and not widely available. One other drug, mipomersen sodium (Kynamro®), is available for patients with HoFH as a weekly subcutaneous injection as an adjunct to lipid-lowering drugs and diet to reduce low-density lipoprotein cholesterol (LDL-C), apolipoprotein-B (apo-B), total cholesterol, and non–high-density lipoprotein cholesterol (non–HDL-C).[32,33] Effective oral, self-administered therapy is needed.

Intervention: Lomitapide (Juxtapid™) is a microsomal triglyceride transfer protein (MTP) inhibitor that is indicated as a daily oral therapy for treating HoFH.[34-36] MTP is a lipid transfer protein that assists in assembling two lipoproteins: chylomicrons and very-low–density lipoproteins (VLDLs). MTP assists in the assembly by transferring triglycerides onto apo-B, an essential component of chylomicrons and VLDL.[37] In essence, MTP binds and shuttles individual lipid molecules from the site of their synthesis (in either the intestine or the liver) to an emerging apo-B molecule, which then forms a chylomicron in the intestine or VLDL in the liver.[37,38] Lomitapide prescribing information advises to begin treatment at 5 mg once daily and to escalate dosage gradually based on acceptable safety and tolerability to 10 mg daily after at least 2 weeks; dosage may be increased at a minimum of 4-week intervals, to 20 mg, 40 mg, and up to the maximum recommended dose of 60 mg daily.[39]

The manufacturer claims that "if insufficient lipid is transferred to the apo-B molecule, the emerging apo-B is destroyed and lipoprotein secretion is inhibited;" therefore, "inhibition of MTP activity prevents both hepatic VLDL and intestinal chylomicron secretion, and consequently lowers plasma lipids."[37]

Clinical trials: FDA approval of lomitapide was based on review of a trial that evaluated the drug in 29 patients with HoFH.[40,41] The median dose was 40 mg per day. Lomitapide reduced LDL-C concentrations by a mean of 50% at 26 weeks from baseline. By week 56, LDL-C concentrations remained reduced by 44% (95% confidence interval [CI], -57 to -31; $p<0.0001$). At week 78, LDL-C concentrations were reduced by 38% (-52 to -24; $p<0.0001$). In the trial, the most commonly reported adverse events were gastrointestinal symptoms. Four patients had aminotransaminase levels measured at more than five times the upper limit of normal; the increase in aminotransaminase levels resolved after dose reduction or temporary halt of lomitapide therapy, but remains a concern for patients on therapy. During the trial, researchers reported that no patient permanently stopped lomitapide because of liver abnormalities.[40,41]

Manufacturer and regulatory status: Lomitapide is manufactured by Aegerion Pharmaceuticals, Inc., of Cambridge, MA.[37] In December 2012, FDA approved lomitapide capsules for marketing as an adjunct to a low-fat diet and other lipid-lowering treatments, including LDL apheresis where available, to reduce LDL-C, total cholesterol, apo-B, and non–HDL-C in patients with HoFH.[41] Lomitapide has boxed warnings on its product label advising of a risk of severe liver toxicity (as does the injectable drug for HoFH, mipomersen sodium).[32,39,42] Likewise, it (and mipomersen) is available only in concert with a Risk Evaluation and Mitigation Strategy (REMS) program.[32,39,42] A REMS program requires the manufacturer to certify prescribing physicians and dispensing pharmacies to use the drug and to document safe-use conditions, including a prescription authorization form for each new prescription.[32] For lomitapide, the program also requires that liver

function tests be performed in patients before administration and at intervals during and after administration.

The company must also conduct three postmarketing studies for lomitapide: an animal study to evaluate potential drug toxicity in pediatric patients; a long-term patient registry to determine long-term safety; and an enhanced pharmacovigilance program to monitor reports of malignancy, teratogenicity, and hepatic abnormalities.[41]

In May 2013, Aegerion announced that the European Committee for Medicinal Products for Human Use had adopted a positive opinion with a unanimous vote recommending a marketing authorization in the European Union for lomitapide (to be marketed as Lojuxta™) capsules for a similar indication.[43] In August 2013, Aegerion announced that it had received approval from the European Commission.[44]

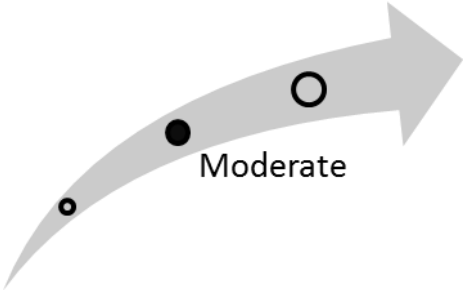
Diffusion: The company reports of the drug's sale through the third quarter of 2013 have exceeded investor analyst and industry projections by about 25%. The company indicated that new prescription rates were accelerating and patient discontinuation of therapy was less than 10% during the first half of 2013; medication adherence rates were stated to be 80% to 90%.[45]

CMS does not have a national coverage determination for lomitapide, so coverage is at the discretion of local Medicare D prescription drug plans. Representative, private, third-party payers that include lomitapide in their drug formularies have precertification and step-therapy policies in place that govern coverage of the drug.[46-48] These payers generally place quantity limits on the drug and require annual recertification and documentation of patients' positive clinical response from lomitapide before allowing prescription renewals.[46-48] GoodRx.com, a U.S.-based, online aggregator of prescription-drug prices, listed retail prices for a 30-day supply of lomitapide at various pharmacies ranging from $25,614 for 5 mg tablets to $27,282 for 20 mg tablets with the use of a coupon (as of November 2013).[49] Thus, the annual per-patient retail cost is more than $307,000.

Clinical Pathway at Point of This Intervention

According to the National Human Genome Research Institute, first-line treatment for patients with HoFH includes lifestyle changes (e.g., diet, exercise) and drug therapy with cholesterol-lowering medications (e.g., statins, bile acid sequestrants, ezetimibe, niacin, gemfibrozil, fenofibrate).[50] For these patients, these therapies are often insufficient, and more aggressive treatment is needed, including periodic apheresis or, possibly, a liver transplant.[50] The FDA-approved indication for lomitapide is as an adjunct to a low-fat diet and other lipid-lowering treatments to reduce LDL-C, total cholesterol, apo-B, and non–HDL-C in patients with HoFH.[41]

Figure 2. Overall high-impact potential: lomitapide (Juxtapid) for treatment of homozygous familial hypercholesterolemia



Overall, experts agreed that for the relatively small number of patients with HoFH, lomitapide has moderate to strong potential to fill the current treatment gap between conventional lipid-lowering drugs (e.g., statins) and invasive, resource-intensive treatments such as apheresis and, in

rare instances, liver transplantation. As an oral rather than injectable drug, lomitapide would likely be adopted widely by physicians for the target population, experts agreed, and they thought that a majority of patients would likely accept the drug as long as their out-of-pocket costs were not prohibitive. Experts generally believe that lomitapide use would be unlikely to disrupt the health care delivery infrastructure or disease management practices for this patient population. Based on this input, our overall assessment is that this intervention is in the moderate high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical, research, health systems, and health administration backgrounds, offered perspectives on this technology.[51-56] Please note the material that experts were given on this topic for comment had been completed shortly before FDA approval, thus their comments do not reflect all the postapproval information (e.g., REMS program requirement, pricing, formulary information) that became available months after approval. Expert comments will be sought in early 2014 on updated information on this topic. Two reviewers declared potential conflicts of interest (COIs). One clinical expert reported treating patients with HoFH, but did not consult for any drug manufacturers.[56] Another clinical expert reported a potential COI as a consultant for drug developers and a clinical trial investigator of lipid-lowering drugs, although not specifically related to patients with HoFH.[54] These potential conflicts of interest are balanced by experts who reported no COIs. We have organized the following discussion of expert comments according to the parameters on which experts commented.

Unmet need and health outcomes: For the small population of patients with HoFH, no effective pharmacologic therapy has been available to bridge the gap between conventional lipid-lowering drugs (e.g., statins) and the need for apheresis or, in rare instances, liver transplantation, the experts noted. Four experts suggested that lomitapide holds potential to improve patient health, at least moderately, given the significant reduction in LDL seen in the trial and especially given the lack of other effective drug therapies in cases in which conventional drugs do not adequately lower LDL. But two experts believe the data were insufficient to estimate the drug's true potential health benefit, with one expert noting that available data suggested a gradual drop in potential efficacy in cholesterol reduction from about 50% at 6 months to 38% at 1.5 years after therapy initiation. Despite these reservations, all experts agreed that lomitapide has moderate to strong potential to fill the unmet need in effective treatments to reduce LDL in HoFH, given that it may bridge the gap between conventional lipid-lowering drugs and invasive treatments that are costly, labor-intensive, and may not be readily accessible to patients with this rare condition.

Acceptance and adoption: Physicians would be likely to widely adopt lomitapide for the targeted population of patients with HoFH, the experts agreed. (Note: The company's third-quarter 2013 report of sales that have exceeded projections by 25% now confirms this view, despite the drug's high cost.) One clinical expert cautioned against inappropriate overuse of the drug among the broader population of patients with elevated cholesterol not due to a genetic defect as in HoFH, because lomitapide has been associated with an increased risk of liver-related adverse effects.[54] A majority of patients would likely accept lomitapide if their physicians advise it, as long as the (out-of-pocket) cost to patients of lomitapide therapy is not cost-prohibitive, the experts thought.

Health care delivery infrastructure and patient management: Overall, most experts who provided comments thought that using lomitapide would create little to no disruption to the health care delivery infrastructure or disease management practices for this patient population. But two experts with clinical and health systems backgrounds anticipated that lomitapide would have a positive, disruptive effect on HoFH patient management by supplanting labor- and resource-

intensive apheresis care and, less commonly, liver transplantation.[54,55] Patient self-administration and office-based physician followup to monitor treatment efficacy and identify possible treatment-related liver problems would also make care less burdensome, thought these two experts.[54,55]

In evaluating lomitapide's potential impact on treatment costs, expert opinion was divided. Three experts thought that lomitapide would cost substantially more than conventional lipid-lowering drugs, but would still most likely cost less than apheresis or liver transplantation in the long term. (Annual costs of the drug were not available to experts at the time they offered their opinions, but are now more than $307,000 per patient per year.) Other experts anticipated that adding lomitapide would represent overall, a moderate, incremental increase in treatment costs for this population. One expert with a health systems background expected that third-party payers would require prior authorization to use lomitapide to help control overuse in lower-risk populations with elevated cholesterol levels.[55]

Health disparities: Lomitapide use would have limited potential to affect health care disparities in treating patients with HoFH, according to the opinions of four experts. But two experts, with clinical and systems backgrounds, suggested that if lomitapide could replace resource-intensive, clinic-based treatment (apheresis) with a self-administered, oral drug therapy, it might reduce disparities by affording more patients access to treatment for HoFH, assuming they have prescription drug insurance and that third-party payers provide coverage.[54,55,57]

Heart Failure Intervention

Portable Freedom Driver for In-Home Support of the Total Artificial Heart

Unmet need: Traditionally, artificial heart technology has involved using large, hospital-based pneumatic driver systems that require patients to be hospitalized and tethered to a driver console. The standard 400-pound console powers the implantable components while patients await availability of a suitable donor heart.[58,59] An option that would allow these patients to leave the hospital and receive artificial-heart support at home while awaiting a donor heart has the potential to lower treatment costs and improve quality of life.[60]

Intervention: The temporary Total Artificial Heart (TAH-t) is a biventricular, implantable device that functions in place of the two failing ventricles and four valves of a failing heart by pumping blood to both the pulmonary and systemic circulations via a conventional external pneumatic driver system.[61,62] The system is large and cumbersome and requires patients to remain hospitalized while awaiting a donor heart.[60] The Freedom Driver is a wearable pneumatic driver designed to power the TAH-t and is intended to allow patients receiving the TAH-t to leave the hospital and live at home while awaiting a donor heart. The patient wears/carries the 13.5 lb pneumatic driver in a backpack or shoulder bag. The driver is powered by two onboard batteries that can be recharged with an automobile adapter or a standard electrical outlet. As with conventional, large, hospital-based pneumatic driver systems, the Freedom driver is connected to the implantable TAH-t by a flexible pneumatic driveline that passes through the patient's skin in the left chest just below the ribs. The driver flashes a light or sounds an alarm when the system requires the user's attention.[60]

Clinical trials: Literature searches have not identified any completed published clinical trials using the Freedom driver, although the company has reported some preliminary results for 41 patients in the Freedom Driver IDE trial. The clinical experience of one individual patient has been published as a case summary.[63]

A 60-patient SynCardia Freedom Driver System Study, an FDA-approved IDE trial, is in progress and was scheduled for completion in October 2013.[59] The company reported that as of October 2013, 86 TAH-t patients had been enrolled in the Freedom driver clinical study (including five patients under compassionate use).[60] Of these 86 patients, 62 had been discharged home using the Freedom portable driver. The Freedom Driver IDE trial requires a minimum of 30 discharges with the portable driver.

One published case report is available in the clinical literature on the Freedom driver; the case report recounts use in a 61-year-old patient who was given the artificial heart with Freedom driver, which enabled him to take several day trips with his wife outside the hospital until he eventually received a human heart transplant.[63] Manufacturer press releases have also been issued periodically on individual patients. For example, the company reported on May 30, 2013, that a 35-year-old man treated at the University of Arizona Medical Center was discharged home and supported for about 62 days with the Freedom driver before undergoing heart transplantation.[64] The manufacturer issued three other press releases in 2013 relating limited information about three other men who were supported with the Freedom driver: a 31-year-old man treated at Intermountain Medical Center (Salt Lake City, UT; March 21, 2013),[65] a 74-year-old man treated at Penn State Hershey Medical Center (Hershey, PA; January 15, 2013),[66] and another 35-year-old man, treated at Ronald Reagan UCLA Medical Center (Los Angeles, CA).[67] However, these news releases did not specify how long the men had been supported with the Freedom portable driver. In August 2013, the manufacturer issued a press release regarding a European patient who exceeded 2 years' use with the Freedom portable driver.[68]

Manufacturer and regulatory status: SynCardia Systems, Inc., of Tucson, AZ, makes the TAH-t and Freedom Driver. In October 2004, FDA approved the TAH-t as a bridge to transplant.[69] The portable Freedom Driver is under evaluation in an FDA-approved IDE trial.[60] In March 2010, SynCardia received Conformité Européene (CE) mark approval to market the Freedom driver in the European Union for use with the SynCardia TAH-t.[70]

Diffusion: The company reported that as of November 2013, 1,200 SynCardia Total Artificial Hearts had been implanted worldwide, and a subset of these (86 noted above) have used the Freedom driver.[71] The driver is available only through the IDE trial or under compassionate use at this time in the United States. The company has periodically distributed limited, anecdotal patient outcomes information in press releases.

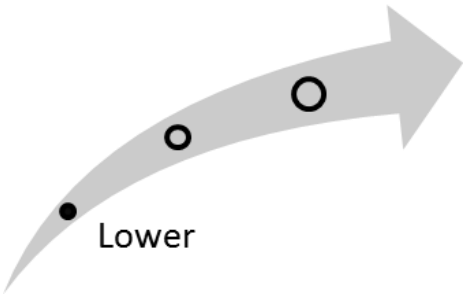
Costs for the portable driver system have not been established in the United States. Total cost of care for patients with artificial hearts using the portable driver at home would be expected to be considerably lower than those of hospitalized patients with artificial hearts. However, ambulatory patients would need regular home visits from nurses trained in use of the device as well as followup clinic visits with specialist physicians to monitor device function and patient health status. Further, as with hospital-based pneumatic drivers, home use of the portable driver would require the immediate availability of a backup driver in case the primary unit fails.

Reported costs for TAH-t kit are about $124,700; the kit includes a patient simulator for physician training, tubing, and surgical disposables in addition to the device itself. The external control console costs about $92,000. Hospitals must also maintain a continuously available backup control console. Hospitals may be able to rent the control consoles as part of an annual service agreement with the manufacturer. Staff training costs to meet manufacturer's device-related certification requirements are an estimated $98,000 in addition to device costs.[72,73]

Clinical Pathway at Point of This Intervention

ACC/AHA clinical guidelines identify ventricular assist device (VAD) implantation and cardiac transplantation as the only established surgical treatments for end-stage heart failure.[74] The portable driver system is intended to complement TAH-t use.[60] As a bridge to transplantation, the TAH-t with the Freedom driver would complement heart transplantation. Some left ventricular assist devices that are compatible with portable driver systems for in-home use could compete with the TAH-t and Freedom driver as a bridge to transplantation.

Figure 3. Overall high-impact potential: Portable Freedom Driver for in-home support of the temporary Total Artificial Heart



Although the patient population for which this device is intended is small, and in-hospital driver systems already exist to support patients with a TAH-t, a portable driver for the TAH-t system has the potential to dramatically improve patient quality of life while awaiting a transplant and to dramatically shift the care setting from inpatient to outpatient, experts commenting on this intervention agreed. Experts also thought that this device has potential to reduce costs associated

with lengthy hospital stays, although its outpatient use would require resources, such as training for staff and home caregivers/family members. Based on this input, our overall assessment is that this intervention is in the lower end of the high-impact-potential range.

Results and Discussion of Comments

Seven experts, with clinical, research, and health systems backgrounds, offered perspectives on this intervention.[75-81] We have organized the following discussion of expert comments according to the parameters on which experts commented.

Unmet need and health outcomes: Although experts noted that the intended patient population for this device is small, they generally agreed that an important unmet need exists for a driver system that would allow patients to be discharged home while awaiting a heart transplant. Experts viewed this device's greatest potential benefits to be improving patient quality of life and decreasing costs of care by enabling patients awaiting a heart transplant to be discharged to home.

Because patients using this device can return home to live, it could provide psychological benefits (increased independence and quality of life), the experts generally thought. They also believe a potential health benefit would arise from increased mobility. Some experts suggested a further health benefit might be realized by reducing risk of health care–acquired infection by getting patients out of the inpatient hospital setting. Some experts likened this technology's potential to that of ventilators and VADs, which have migrated from inpatient care to outpatient care and a home setting with positive results.

Acceptance and adoption: If good outcomes are demonstrated from the ongoing trial, both clinicians and patients would readily adopt this technology because of its potential for lower costs and improved quality of life and health status, the experts thought. Although several experts also noted that extensive training (on the part of both hospital staff and patient home caregivers) would be required for diffusion of this device, they did not think this would be a barrier to uptake.

Health care delivery infrastructure and patient management: Experts noted that shifting patient care from an inpatient setting to the home is important and would likely lower costs significantly, given the expense of continuous, long-term inpatient care. Experts noted, however, that few data are available yet to support this presumption. Some experts anticipated that moving these patients home may simply shift care and costs and would increase the need for home-care personnel with experience in treating patients who have received artificial hearts.

The shift in care setting has potential to change case management. The shift could "substantially impact the aftercare community and require additional collaboration and coordination between inpatient and outpatient facilities," said one expert with a health systems background, reflecting others' opinions as well.[78] A clinical expert expected a larger disruption in current management of patients who have artificial hearts, noting, "This [device] will require patients and families to learn and take ownership – and in turn family knowledge, attitudes, availability, and dynamics all have to be evaluated for implant suitability."[77]

Experts generally expected disruptions to the way these patients are currently managed, with moderate overall disruption to clinical patient management and larger disruption for patients and their home caregivers/families, who would need to play a more active role in caring for these patients at home than if the patient remained in hospital.

Health disparities: Experts generally agreed that the portable Freedom driver was likely to have minimal effect on health disparities. One expert with a research background suggested that the technology might potentially decrease access to care "due to the need for extensive caregiver support and training, [and] proximity to facilities that could handle this level of care.[79]

Hypertension Intervention

Catheter-Based Radiofrequency Ablation (Symplicity System) Renal Denervation for Treatment-Resistant Hypertension

Unmet need: Lowering high blood pressure has been associated with lower rates of stroke, heart attack, and heart failure, and many pharmacotherapies are available for treating hypertension.[82,83] Strict adherence to recommended medical therapy can provide effective blood pressure control for most patients.[84] However, even in highly motivated and medication-adherent patients, several factors may affect the efficacy of antihypertensive therapy, including interaction with other prescription and over-the-counter medications, as well as various foods, vitamins, and herbal supplements.[84] Because uncontrolled, medically refractory hypertension is associated with high morbidity and mortality, novel interventions for treating this condition are needed.[83]

Intervention: The sympathetic nervous system is known to contribute to blood pressure increases.[85,86] Afferent renal sensory nerves, which carry signals from the kidneys to the central nervous system, also play a role in promoting sympathetic outflow and are considered additional contributors to hypertension.[87] Surgical disruption of renal sympathetic nerves has been explored for decades as a potential therapeutic intervention for hypertension.[88] Earlier approaches usually involved radical sympathetic denervation, an open surgery procedure that reduced blood pressure in some patients but was associated with serious perioperative and long-term complications (e.g., bowel, bladder, erectile dysfunction; postural hypotension) and therefore abandoned.[88] The Symplicity® Renal Denervation System™ is a minimally invasive RF ablation system intended to replicate the blood pressure improvements seen with radical sympathetic denervation but avoid its associated side effects.[88]

The manufacturer purports that bilaterally denervating the renal nerves with the Symplicity system can achieve a sustainable decrease in blood pressure.[89] The manufacturer states that the system comprises two components: a generator that automatically controls the RF energy delivery by the clinician and a hands-free switch to activate the RF energy delivered through a catheter to the renal artery. The system is compatible with 6 French (Fr) diameter guide catheters.[90-92]

The clinician performs the denervation procedure in a catheterization laboratory with the patient under conscious sedation; the procedure takes about 40 minutes.[90,93,94] The manufacturer states that to perform the procedure, a physician introduces the catheter through the femoral artery via a guide catheter and threads it to the renal artery. The catheter's tip is placed against the arterial wall, and clinicians deliver RF energy to the surrounding sympathetic nerves; the energy is managed via a computer-controlled algorithm.[90] The physician may apply up to six ablations, lasting up to 2 minutes each, within each renal artery.[94] The manufacturer states that because the one-time procedure does not involve a permanent implant, patients recover and return to their activities of daily living quickly.[89]

Clinical trials: Four trials (some completed, some ongoing) known as the Symplicity HTN trials have been planned for this technology. HTN-3 and HTN-4 are ongoing. In March 2013, investigators reported 24-month results from Symplicity HTN-2, the first randomized, controlled, crossover trial investigating renal denervation.[95] Among 40 patients randomly assigned to receive Symplicity renal denervation, blood pressure dropped significantly at 24 months by 29/10 mm Hg from 178/97 mm Hg at baseline ($p<0.01$). Among 26 randomly assigned control group patients who later crossed over to receive renal denervation after 6-month primary endpoint assessment (crossover group), average blood pressure dropped at 24 months by 35/13 mm Hg from 178/98 mm Hg at baseline ($p<0.01$). Investigators noted that average blood pressure reductions at 24 months had been preserved compared with reductions achieved for both groups at 6, 12, and 18-month followup. Further, investigators observed no device-related serious adverse events, no late vascular

complications, and no significant declines in kidney function at 24 months compared with patients' baseline values. Investigators also observed that pulse pressure improved significantly by -18.5 mm Hg from baseline for the initial treatment group ($p<0.01$) and by -22.5 mm Hg from baseline for the crossover group ($p<0.01$). Pulse pressure is the numeric difference between systolic blood pressure (SBP) and diastolic blood pressure (DBP); higher pulse pressures have been associated with increased cardiovascular complications, especially in older patients.[95]

Also in May 2013, Symplicity's manufacturer announced 6-month safety results from 617 patients in the Global Symplicity Registry (which includes patients outside the United States).[96] Investigators reported no major complications or serious adverse events related to Symplicity renal denervation. Two patients experienced vascular complications at the catheter access site immediately after the procedure. Angiography revealed a renal vessel irregularity in 9% of patients after the procedure due to the application of RF energy to the vessel wall. However, no detected vessel irregularities interfered with brisk renal blood flow. Investigators surmised that all vessel irregularities had resolved shortly after the procedure.[96]

Besides the registry's primary safety analysis, analysis of available data for the secondary efficacy endpoint at 6 months showed renal denervation significantly reduced both office and ambulatory blood pressure measurements compared with baseline measurements. Patients with SBP of more than 180 mm Hg and DBP of more than 100 mm Hg (n=17) showed an average reduction of 30/16 mm Hg from baseline at 6 months (SBP $p<0.0002$; DBP $p<0.0008$). Among patients with SBP of more than 160 mm Hg (or more than 150 mm Hg in diabetic patients) (n=114), blood pressure dropped by an average of 18/9 mm Hg from baseline at 6 months ($p<0.0001$). Among 29 patients who also had 24-hour ambulatory blood pressure measurement (n=29), blood pressure fell by an average of 11/4 mm Hg from baseline ($p<0.0001$).[96]

A 2012 health economics study reported that catheter-based renal denervation is cost-effective and may lower cardiovascular morbidity and mortality in patients with treatment-resistant hypertension.[97]

Manufacturer and regulatory status: Medtronic, Inc., of Minneapolis, MN, makes the Symplicity system, which it acquired when it bought developer Ardian, Inc., in 2011. The system is available only for investigational use in the United States but is approved for marketing in the European Union and Australia.[98] Several other renal denervation systems are in development. St. Jude Medical, Inc. (St. Paul, MN), received European marketing approval for its EnligHTN™ renal denervation system in May 2012.[99] Boston Scientific is developing its Vessix™ Renal Denervation System, which is under evaluation in early phase clinical trials in Europe.[100]

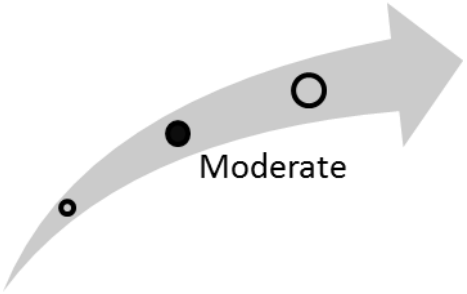
Diffusion: On May 23, 2013, Medtronic announced it had completed patient random assignment for Symplicity HTN-3, a 530-patient, phase III trial intended to support a PMA application to FDA for its Symplicity renal denervation system.[101] The company also announced that the Symplicity device would be evaluated under the relatively new FDA-CMS parallel review program, which enables CMS to begin a national coverage determination process for an intervention while FDA conducts its safety and efficacy review. Medtronic reported that Symplicity HTN-3 trial data would comprise a substantial component of the parallel review.[101] U.S. pricing of the Symplicity technology has not been reported yet.

Clinical Pathway at Point of This Intervention

According to the most recent report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, lifestyle modifications (e.g., weight and diet management) are the initial interventions used in patients with hypertension. If lifestyle changes do not result in satisfactorily controlled blood pressure, pharmacotherapy is indicated.[82] Medical

management of hypertension includes thiazide-type diuretics, used alone or in combination with one of several classes of antihypertensive agents (e.g., angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta blockers, or calcium channel blockers).[82] If the Symplicity Renal Denervation System is approved for use in the United States, it is likely to be positioned for use in treatment-resistant hypertension that has not adequately responded to three or more antihypertensive medications. These medical therapies are likely to be used in conjunction with the renal denervation procedure.[90,102]

Figure 4. Overall high-impact potential: catheter-based radiofrequency ablation (Symplicity System) renal denervation for treatment-resistant hypertension



Experts commenting on this intervention agreed that it has potential to fill an important gap in treating hypertension and would likely be accepted by clinicians and patients. However, this intervention's potential impact is tempered by the need for longer-term outcomes data. The procedure is expected to be easily incorporated into the existing health care infrastructure (i.e., using a catheterization laboratory). Several experts agreed that the intervention would likely increase the number of patients treated in catheterization labs and would represent a shift in patient management away from medical therapy to a procedure. Based on this input, our overall assessment is that this intervention is in the moderate high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical, research, health systems, and health administration backgrounds, offered perspectives on this intervention.[103-108] We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: The need for effective interventions for treatment-resistant hypertension is important, experts agreed, because of the size of the affected population, the morbidity and mortality associated with the condition, and the dearth of available treatments once pharmacotherapy fails to achieve desired outcomes. The experts were cautiously optimistic that this intervention is likely to improve patient health, citing the promising efficacy data that have been collected to date. However, several experts noted that the available data are limited, and several experts want to see longer-term studies to determine whether the reduction in blood pressure observed in trials translates to improved clinical outcomes and to further clarify the safety profile of the intervention.

Acceptance and adoption: Expert opinions varied regarding the degree of acceptance of this intervention by both clinicians and patients. Some experts thought that clinicians would likely adopt the technology because alternative treatments do not exist for this population and because the intervention requires only a one-time procedure. On the other hand, some experts suggested that the invasiveness of the procedure might pose a barrier to acceptance by some patients. Additional data from the phase III U.S. pivotal trial and the ongoing global registry are eagerly anticipated.

Health care delivery infrastructure and patient management: Most experts suggested that this intervention would not especially disrupt health care infrastructure because the procedure will be performed in a catheterization laboratory, which as one clinical expert stated, "could accommodate patient volume, assuming it is an outpatient procedure, is not associated with significant complication, and requires a single sitting application."[103] However, several experts agreed that this intervention would likely increase the number of patients seeking services from catheterization labs and would represent a shift in patient management away from office-prescribed medical therapy over the long term should this intervention be shown to reduce the need for ongoing hypertension pharmacotherapy.

Most experts expected this intervention would have a moderate effect on health care costs. Although the initial procedure will be associated with an initial upfront cost, some of this initial outlay could be offset by the potential for future savings, if the intervention is proved to improve patient health.

Health disparities: Experts were about evenly divided regarding renal denervation's potential to affect health disparities. Experts who thought the technology would have minimal to no impact on changing disparities anticipated that the technology would be likely expensive and, thus, could increase disparities among patient populations with less access to care, particularly African Americans. One clinical expert added that the therapy may not be covered by some health plans, at least initially, potentially creating further disparities among patients without health insurance; however, "it may help those without prescription drug coverage if it decreases the number of medications they need."[107] Another clinical expert surmised that if this technology shows long-term effectiveness, it could potentially have a large effect on reducing disparities if poor patients have access to it because "poor patients often have trouble getting medications and are often noncompliant."[103]

Valve and Structural Disorder Interventions

Transcatheter Aortic Valve Implantation (CoreValve) for Treatment of Severe Aortic Stenosis

Unmet need: The gold standard for treating aortic stenosis has been open surgical replacement of the valve with a mechanical valve or a bioprosthetic valve.[109-111] However, open-heart surgery is typically not an option for patients at high risk of developing surgical complications.[109,110,112] Medical therapy is typically the only therapeutic option for these patients; however, medical therapy is often ineffective in this population, and mortality tends to be high.[113-115]

Intervention: Manufacturers have developed a catheter-based valve implantation technology that allows clinicians to implant diseased aortic valves using minimally invasive techniques. Transcatheter aortic valve implantation (TAVI; also known as transcatheter aortic valve replacement [TAVR]) is intended to extend the therapeutic benefit of surgical aortic valve implantation to patients ineligible for surgery or at high risk of surgical complications.[110,112,116-118]

The CoreValve® System is being investigated in IDE trials in the United States for treating severe aortic stenosis.[119] The system is intended for use in patients who are not surgical candidates or who are at high risk of developing surgical complications. The system features a porcine pericardial tissue valve mounted in a self-expanding, hourglass-shaped, nitinol-alloy mesh frame. The bioprosthetic valve is deployed using an 18 Fr diameter delivery catheter with a set of disposable catheter-loading components.[120,121]

According to CoreValve's manufacturer, typical implantation procedures last about 1–3 hours, and patients are sedated. The clinician guides a catheter into the heart, then threads a balloon catheter through the guide catheter into the heart. Once the balloon is positioned in the aortic valve, it is inflated to prepare for implanting the CoreValve. Using imaging equipment to direct placement, the clinician situates the CoreValve over the diseased aortic valve; in some cases, the diseased valve is completely removed before the CoreValve is placed. After the valve is placed, the catheter is removed, and the incision is closed. The manufacturer states that the typical hospital stay following a TAVI procedure is 3–5 days.[122]

One of three other, more direct access routes can be used when the transfemoral route is impractical or undesirable because of severe, systemic vascular disease that impedes catheter navigation from the femoral artery. In the transapical approach, the physician makes a small incision between the ribs to access the heart apex (bottom) and advances the delivery catheter through the apex into the left ventricle to reach the aortic valve.[123,124] In the subclavian approach, the physician inserts a catheter under the clavicle into the subclavian artery to deploy the aortic valve.[122] The transaortic approach allows a physician to insert the delivery catheter into the aorta through the ribs using either a mini-thoracotomy in the second intercostal space or an upper hemisternotomy.[125,126] Valve deployment with alternate access routes is similar to that in the transfemoral approach, once the delivery catheter is positioned.

Clinical trials: In May 2013, the manufacturer reported 1-year results from the CoreValve ADVANCE Study that suggested TAVI had low rates of mortality and stroke and improved hemodynamics (blood flow) in patients with severe aortic stenosis considered to be at high risk of surgical complications.[127] The CoreValve Advance International Post Market Study (CoreValve is approved in Europe) is a prospective, observational study intended to evaluate CoreValve TAVI procedures in patients outside of a clinical trial setting. Among the 996 treated patients overall, investigators reported on 806 of 824 patients (97.8%) for whom 1-year followup data were available. At 1 year, the all-cause mortality rate was 17.9%, the cardiovascular mortality rate was 11.7%, and the combined stroke rate was 4.5%, including a 2.3% minor stroke rate and a 2.3% major stroke rate.

In the study, investigators also observed substantial improvement in disease symptoms. At baseline, only 20% of patients were classified as class I or class II on the New York Heart Association (NYHA) scale of functional limitations due to heart failure. However, 30 days after TAVI, 85% of patients were classified as NYHA class I or II, and at 1 year, 87% of patients were classified as NYHA class I or II.[127] The NYHA scale has four major classifications, from I to IV; lower classifications indicate better health.

In October 2013, the manufacturer presented positive pivotal trial data that suggested significantly reduced rates of death or major stroke at 1 year; however, full trial results are not yet available.[128]

Manufacturer and regulatory status: Medtronic makes the CoreValve System. The valve is not yet approved for marketing in the United States, but CoreValve received CE mark in May 2007 for the CoreValve Percutaneous ReValving™ System for treating patients at high risk of experiencing complications with surgery.[129] Medtronic received a CE mark in September 2012 for the newest valve addition to the system, the CoreValve Evolut, a 23 mm valve that can fit an aortic annulus size of 18 mm. The CoreValve System now has four valve sizes (23, 26, 29, and 31 mm) to fit aortic annulus sizes that range from 18 mm to 29 mm.[129] FDA granted Medtronic an IDE for its U.S.-based CoreValve trial in October 2010.[130] In October 2013, following the announcement of positive pivotal trial data, FDA announced that it would no longer require an advisory panel. CoreValve FDA approval is anticipated in early 2014.[128]

Diffusion: In May 2012, CMS released a national coverage determination for TAVI, stating that CMS "covers transcatheter aortic valve replacement (TAVR) under Coverage with Evidence Development (CED)" when the procedure is used for "the treatment of symptomatic aortic valve stenosis when furnished according to an FDA approved indication" and when certain conditions are met.[131] The coverage determination listed criteria for the required infrastructure, interdisciplinary team members, number of procedures needed to achieve and maintain proficiency, and other requirements. The determination also covers the CoreValve devices used in the context of the IDE trial.

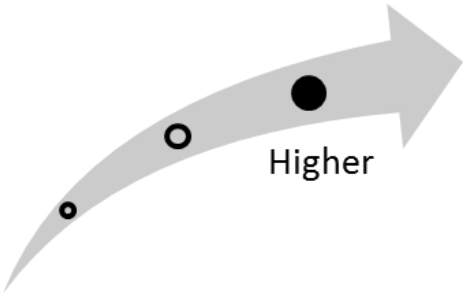
As of December 2013, a search of representative, private, third-party payers that publish their coverage policies online showed they generally cover TAVI procedures for patients who are not surgical candidates and that the payers have adopted requirements that are similar to or the same as Medicare's requirements; however, some of these payers have not followed suit and have not expanded coverage policies to include patients who are eligible for open surgery but at high risk of complications.[132-137]

Although costs of the CoreValve have yet to be determined, one estimate predicts the device will cost about $30,000.[128] Device and procedure costs are anticipated to be competitive to the Edwards Lifesciences Corp.'s Sapien TAVI already on the market, unless CoreValve shows some significant advantage over that valve.

Clinical Pathway at Point of This Intervention

According to 2006 guidelines by ACC/AHA, aortic valve replacement is considered the surgical treatment of choice for most adults with severe aortic stenosis who are candidates for open heart surgery.[138] For patients who are not candidates for open surgery and have a poor prognosis, medical management or aortic balloon valvuloplasty were the only options. However, these options do not provide full relief of aortic stenosis symptoms; the only definitive treatment is aortic valve replacement.[109,110,139] The advent of TAVI provides a new option for patients with severe aortic stenosis who are not candidates for surgery or who are at high risk of surgical complications and would otherwise have no treatment options.[112,140-142]

Figure 5. Overall high-impact potential: transcatheter aortic valve implantation (CoreValve) for treatment of severe aortic stenosis



Experts commenting on this intervention agreed that it offers an important new treatment modality for patients who have few options. Experts thought that this intervention would improve patient health outcomes, and they thought an increase in case volume would be seen as this intervention diffuses. Experts experienced in the procedure pointed out that establishing a program puts a significant strain on conventional resources and requires additional infrastructure to evaluate potential patients and perform the procedure. Experts agreed that the intervention has the potential to both increase (in the short term) and decrease (in the long term) health care costs. Based on this input, our overall assessment is that this intervention is in the higher end of the high-potential-impact range.

Results and Discussion of Comments

Seven experts, with clinical, research, health systems, and health administration backgrounds, offered perspectives on the CoreValve technology.[143-149] We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: The unmet need addressed by this intervention is extremely important, the experts concurred, citing the large number of patients who would be affected and the fact that options are very limited for this population. As one research expert stated, "Limited treatment options exist for patients with aortic valve stenosis who are not candidates for surgery. Living with aortic valve stenosis can seriously compromise quality of life."[145] Further, experts asserted that this patient population is growing as the U.S. population ages and as better techniques for identifying patients with aortic stenosis are developed.

In supporting this intervention's ability to meet the unmet need and improve patient health outcomes, experts were optimistic mostly because of encouraging data from clinical trials but also because it provides an option to a population that has no other effective options available. Further, some experts suggested that over time, this intervention may be extended to patients who are "who would otherwise not be considered candidates for valve replacement," although data on safety and durability of the procedure are needed for this expanded patient population.[146]

Acceptance and adoption: Clinicians who treat these patients would readily accept this technology, the experts thought, considering that no other interventions are available for this patient population. But they thought actual adoption might be relatively slow for centers outside of those that participated in the clinical trials, given the conditions of coverage, infrastructure requirements, and required multidisciplinary teams. Experts also generally thought that patients would accept this procedure because it offers a therapeutic option where previously none existed and because the intervention is considered minimally invasive.

Health care delivery infrastructure and patient management: Experts had differing perspectives about the extent to which this technology will disrupt health care infrastructure and

patient management models. Some experts stated that this intervention could be conducted in existing facilities that have hybrid operating rooms and the necessary interdisciplinary clinical staff, thereby not markedly disrupting current infrastructure. However one clinical expert with experience in the technology stated that for facilities without existing infrastructure, "starting a TAVR program…is a huge undertaking. It is not just adding another procedure, it is adding a whole new program to a medical center. The resource utilization is considerable. The program will put a significant strain on conventional resources and require an additional infrastructure to evaluate potential patients."[147] One notable consequence of this intervention is the shift in care setting for patients who typically would have been treated only with medical therapy. Case volume at centers offering TAVI is expected to rise accordingly, and even if patients referred for evaluation are not candidates for TAVI, the referrals alone are expected to increase patient case load on heart teams that evaluate patients for TAVI eligibility.

Experts were confident that this intervention would a have significant impact on health care costs for payers and hospitals. Costs of care for patients previously treated with medical therapy who are eligible for and undergo TAVI will increase. Also, some experts noted that Medicare reimbursement rates might not cover device and procedure costs, so hospitals might lose revenue on the procedure, although such a loss might be offset by an increase in referrals that end up receiving other non-TAVI treatment (such as open surgery). However, several experts noted that some costs associated with medically managed patients with end-stage disease (e.g., hospitalizations) might decrease after patients undergo TAVI because they would not be expected to need pharmaceutical treatment and because hospitalizations could decrease for complications in patients previously on medical therapy.

Health disparities: Experts generally anticipated that TAVI would not alter health disparities significantly, in part because of the high device and procedure cost as well as the availability, at least initially, limited to centers of excellence with clinical trial experience in TAVI. However, one clinical expert concluded that TAVI might greatly alter disparities in care for very elderly patients with newly discovered severe aortic stenosis, who were essentially "written off" before TAVI became available because of the ineffectiveness of medical therapy.[147]

Transcatheter Mitral Valve Repair (MitraClip) for Treatment of Mitral Regurgitation

Unmet need: Although open surgical repair of the mitral valve is the gold standard treatment for mitral regurgitation (MR), some patients are ineligible for surgery or are poor surgical candidates because of their high risk of developing complications during surgery.[150,151] Left untreated, severe MR can lead to congestive heart failure or potentially life-threatening cardiac arrhythmias.[152] For these patients, a treatment gap exists for an intervention that approximates the therapeutic benefit of open surgical mitral valve repair while minimizing the procedural risks.

Intervention: The MitraClip device is intended to simulate the functional effects achieved by the Alfieri edge-to-edge surgical procedure, an open surgery repair technique used for treating MR.[151] In the Alfieri procedure, a surgeon sutures together the edges of the two opposing mitral valve leaflets at the center of the valve opening, leaving two smaller openings on either side that close more completely than a single large opening.[153] The MitraClip device mimics this procedure by "clipping together" the mitral valve leaflets, rather than using sutures.[151,154]

The MitraClip is an implantable, two-armed, flexible metal clip made of cobalt and chromium and covered in polyester fabric. It is intended to help the mitral valve close more completely, thereby potentially reducing MR.[155] The MitraClip system consists of the clip device, a clip-delivery system, and a steerable guide catheter.

Clip implantation is performed in a catheterization laboratory using fluoroscopic and transesophageal echocardiographic guidance;[151] the patient is placed under general anesthesia, but no heart-lung machine is required.[156] The manufacturer states that recovery typically lasts 1–3 days.[156]

During the device-placement procedure, surgeons advance the guide catheter through the femoral vein into the left atrium and, using the catheter and clip-delivery systems, position the opened clip over the mitral valve. The surgeon advances the clip to the left ventricle and closes its arms, clamping the mitral valve leaflets together. At this point, MR is assessed; if the change in MR is not satisfactory, the clip is repositioned.[156] The implantation procedure requires a trans-septal puncture, which has been called a "crucial early step" in the procedure.

Clinical trials: In 2013, investigators reported 1-year outcomes from 59 patients with severe, symptomatic MR and reduced ejection fraction who received MitraClip therapy.[157] The primary outcomes evaluated were procedural efficacy measured by reduction in MR and improvement in NYHA functional classification. Investigators found that device implantation was associated with reduced MR and improved NYHA functional class, translating into improved 6-minute walk test distance. Patients also demonstrated reductions in the cardiac markers high-sensitive troponin T ($p<0.05$) and NT-proBNP (nonsignificant). Followup echocardiography suggested a reversal in heart enlargement, with reduced left atrial volume and left ventricular end-systolic diameter and increased left ventricular ejection fraction (LVEF). These results were consistent with outcomes of a subgroup of 25 patients with severely reduced LVEF (EF 23±2%; n=25), suggesting that sicker patients also benefitted from MitraClip therapy. Investigators reported 30-day mortality of 2.9%.[157]

Also in 2013, investigators reported outcomes from 117 patients in the GRASP Registry.[158] The primary outcome measures were the rate of major adverse events at 30 days, freedom from death, surgery for mitral valve dysfunction, or grade 3+ or greater MR at 30 days and 1 year. Investigators reported acute procedural success, defined as residual MR grade 2+ or less after MitraClip implantation, in all patients and no procedure-related mortality.

With experience, physicians substantially reduced their procedural times. Procedure times varied widely among cases involving implantation of a single clip and multiple clips.

Major adverse events were reported for four patients at 30 days (4.3%). Thirteen patients experienced increased MR to MR grade 3+ or more at 1 year. At 1 year, no patients required surgery for mitral valve dysfunction. Freedom from death, freedom from surgery for mitral valve dysfunction, or freedom from grade 3+ or more MR was 96.4% at 30 days and 75.8% at 1 year.[158]

Manufacturer and regulatory status: Abbott Laboratories, Abbott Park, IL, makes the MitraClip. In October 2013, FDA granted marketing approval for the MitraClip delivery system for treating significant symptomatic degenerative mitral regurgitation. As part of the approval, FDA is requiring the manufacturer to conduct two postapproval studies to assess long-term safety and efficacy.[159] Preceding the approval, a March 2013 FDA advisory panel had voted on the safety, effectiveness, and risk-benefit ratio of the MitraClip system. The panel had voted 5-3 that MitraClip's benefits outweighed the risks for use in patients who met the criteria specified in the proposed indication: to reduce significant symptomatic mitral regurgitation (MR of 3+ or more) in patients at high risk of complications with open surgery and in whom existing comorbidities would not preclude the expected benefit from treatment. The panel voted 8-0 that available data showed MitraClip to be safe when used for the proposed indication. However, the panel voted 5-4, with the chairperson voting as tie breaker, that there was not "reasonable assurance" from available trial data that the MitraClip procedure would be effective for its proposed indication.[160]

In March 2013, the UK's Medicines and Healthcare products Regulatory Agency (MHRA) issued a medical device alert advising interventional cardiologists and cardiothoracic surgeons of a "risk of death or serious harm" during MitraClip implantation.[161] The MHRA alert advises, "if the Actuator Knob on the Clip Delivery System (CDS) is turned in the wrong direction, this can prevent successful deployment of the clip, leading to the need for open surgical repair."[161]

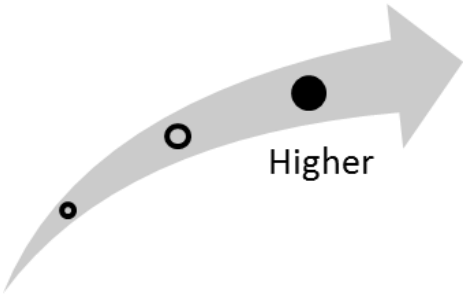
In May 2011 (before the 2013 safety advisory), the manufacturer issued a voluntary device recall in Australia, Europe, Singapore, and other countries where the device had been approved because of issues with the delivery catheter's tip. Although the company resolved the issue and reintroduced the device in those countries, the recall prompted FDA to request additional information and analysis regarding the MitraClip, which the company provided.[162]

Diffusion: The device is just beginning diffusion, given the recency of its approval. Its adoption may be slow initially because of safety alerts in 2013 and product recalls in 2011 that could affect physician and patient acceptance. The availability of reimbursement for the device and procedure also could affect physician acceptance and diffusion. Two representative, private, third-party payers (i.e., Humana, United Healthcare) consider MitraClip therapy investigational at this time and deny coverage for the procedure.[136,163]

Clinical Pathway at Point of This Intervention

The preferred treatment for severe MR is open surgery for valve repair or valve replacement.[150,151] ACC/AHA clinical guidelines recommend surgical mitral repair over mitral valve replacement in most patients because the "valve is suitable for repair and appropriate surgical skill and expertise are available."[138] MitraClip may potentially be positioned as a catheter-based (transcatheter) alternative to surgical valve repair.[150,151]

Figure 6. Overall high-impact potential: transcatheter mitral valve repair (MitraClip) for treatment of mitral regurgitation



Overall, experts agreed this procedure addresses a considerable unmet need and has the potential to improve patient health, although some experts agreed that more data concerning safety and long-term outcomes are needed. Experts' opinions differed somewhat about how much this intervention would disrupt current health care delivery for this condition. Some experts believe the disruption to health care delivery would be limited because the infrastructure to perform the procedure is already in place at many health care facilities offering valve surgery, although other experts believe that the potential increase in numbers of patients seeking treatment for functional MR has potential to cause a large disruption to health care delivery. The majority of experts thought the MitraClip would increase health care costs, but they wanted to see more long-term data to assess whether the device would reduce long-term costs of care for this patient population. Based on this input, our overall assessment is that this intervention is in the higher end of the high-impact-potential range.

Results and Discussion of Comments

Seven experts, with clinical, research, health systems, and health administration backgrounds, offered perspectives on this technology.[164-170] We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: The unmet need for less-invasive interventions to treat MR is important because of the large number of patients with MR who are not candidates for surgical repair, the majority of experts agreed. One expert also noted that patients with secondary MR and significant left ventricular dysfunction would be good candidates for this procedure.[164]

But opinions diverged about the device's potential to fulfill the unmet need. Two experts thought this device has relatively low overall potential to fulfill the unmet need, with one stating that this is just another treatment option for patients with MR.[165] Another expert believes that the procedure is highly risky and that more data demonstrating safe and reliable outcomes would be needed for the device to have a greater potential in fulfilling the unmet need. Conversely, other experts thought that this device holds promise, especially for patients at high risk of developing surgical complications.

Health outcomes could improve with this intervention, most of the experts believe, although they expressed a desire to see more and longer-term clinical data. One expert believes that the MitraClip has great potential to improve health outcomes in both patients with primary MR that originates from the center of the valve and patients with relatively normal valve tissue who have secondary MR due to chamber enlargement or dysfunction.[164] This expert also thought MitraClip might serve as an intermediate treatment for patients with severe dilated cardiomyopathy. But concerns about device and procedure safety were raised by some experts who believe that the

numerous comorbidities seen in these patients would present risk and preclude some patients from achieving greatly improved outcomes.

Acceptance and adoption: Although most experts agreed that the MitraClip implant would entail significant training and a significant learning curve for clinicians, they agreed that if clinical trial data continue to demonstrate benefits and safety of the device, clinical acceptance would follow. Patients would likely accept this minimally invasive therapeutic option for MR if sufficient data of safety and effectiveness is developed, because they lack other options, the experts all agreed. But one expert noted that this procedure is not intended to completely repair mitral valves; therefore, patients who are eligible for open surgery might prefer that option to achieve a complete, rather than partial, repair.[164] Patient acceptance could also be influenced by cost, two experts suggested, but they differed. One expert believes cost could have a positive effect on acceptance because of decreased treatment costs, and the other believes that acceptance would be limited if insurance does not cover the procedure.[165,169]

Health care delivery infrastructure and patient management: The experts offered three perspectives about this intervention's potential impact on the health care system. First, the majority of experts believe availability of this device could increase the number of patients coming to the hospital for a procedure and shift care from outpatient medical management to inpatient care, thus, having a large potential to disrupt the health care delivery system. Conversely, other experts believe that, although increased case volume is a potential disruption, the infrastructure to carry out this procedure is already in place in most cardiac intervention facilities and so it should not greatly disrupt the health care delivery infrastructure. Finally, one expert thought any change in patient management would be gradual and, therefore, would not significantly disrupt the current care pathway.[164]

The device and its related procedure would be expensive and affect overall health care costs, the experts generally agreed. The importance of long-term studies in determining overall impact on health care costs was noted by most experts. But a few experts thought that the MitraClip would affect health care costs only minimally, reasoning that this procedure would be less costly than surgical treatment or long-term care of patients who are not eligible for surgery.

Health disparities: Experts all agreed that this device would have minimal impact on health care disparities. One clinical expert noted, "It's unclear if access to this procedure would be any better than any other interventional procedure…. One benefit might be for patients with poor social circumstances that have to be eliminated [i.e., addressed] as either left ventricular assist device candidates or heart transplant candidates when they become [end]stage because of severe lack of social support or ability to afford or care for themselves."[164]

References

1. Bardy GH, Smith WM, Hood MA, et al. An entirely subcutaneous implantable cardioverter-defibrillator. N Engl J Med. 2010 Jul 1;363(1):36-44. PMID: 20463331
2. Kleemann T, Becker T, Doenges K, et al. Annual rate of transvenous defibrillation lead defects in implantable cardioverter-defibrillators over a period of >10 years. Circulation. 2007 May 15;115(19):2474-80. PMID: 17470696
3. Maisel WH. Semper fidelis--consumer protection for patients with implanted medical devices. N Engl J Med. 2008 Mar 6;358(10):985-7. Also available: http://content.nejm.org/. PMID: 18322280
4. Boston Scientific receives FDA approval of first-in-class S-ICD System for patients at risk of sudden cardiac arrest. [internet]. Natick (MA): Boston Scientific Corporation; 2012 Sep 28 [accessed 2012 Oct 2]. [2 p]. Available: http://bostonscientific.mediaroom.com/2012-09-28-Boston-Scientific-Receives-FDA-Approval-of-First-in-Class-S-ICD-System-for-Patients-at-Risk-of-Sudden-Cardiac-Arrest.
5. U.S. Food and Drug Administration (FDA). FDA approves first subcutaneous heart defibrillator. [internet]. Silver Spring (MD): U.S. Food and Drug Administration (FDA); 2012 Sep 28 [accessed 2012 Oct 2]. [2 p]. Available: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm321755.htm.
6. Boston Scientific Corporation. Effective defibrillation without transvenous leads. [internet]. Natick (MA): Boston Scientific Corporation [accessed 2012 Nov 14]. [1 p]. Available: http://www.bostonscientific.com/cardiac-rhythm-resources/cameron-health/sicd-components.html.
7. S-ICD implant overview. [internet]. Natick (MA): Boston Scientific Corporation [accessed 2013 Apr 16]. [2 p]. Available: http://www.bostonscientific.com/cardiac-rhythm-resources/cameron-health/sicd-implant.html.
8. S-ICD system overview. [internet]. Natick (MA): Boston Scientific Corporation [accessed 2013 Apr 16]. [2 p]. Available: http://www.bostonscientific.com/cardiac-rhythm-resources/cameron-health/sicd-system.html.
9. Subcutaneous implantable cardioverter-defibrillator (ICD). [internet]. Birmingham (UK): EuroScan International Network; 2012 Nov 20 [accessed 2012 Nov 20]. [4 p]. Available: http://euroscan.org.uk/technologies/technology/view/1704.
10. Jarman JW, Todd DM. United Kingdom national experience of entirely subcutaneous implantable cardioverter-defibrillator technology: important lessons to learn. Europace. 2013 Aug;15(8):1158-65. Epub 2013 Feb 28. PMID: 23449924
11. Boston Scientific closes Cameron Health acquisition. [internet]. Natick (MA): Boston Scientific Corporation; 2012 Jun 8 [accessed 2012 Oct 11]. [3 p]. Available: http://bostonscientific.mediaroom.com/2012-06-08-Boston-Scientific-Closes-Cameron-Health-Acquisition.
12. Doctors want Boston Scientific's novel S-ICD system, but supply problems hampering launch. [internet]. MDDI; 2013 Apr 25 [accessed 2013 Dec 6]. [3 p].
13. Boston Scientific 2013 billing and coding guide. Natick (MA): Boston Scientific; 2013 Jan. Subcutaneous implantable defibrillator (S-ICD). p. 6. Also available: http://www.bostonscientific.com/cardiac-rhythm-resources/assets/downloads/reimbursement/2013/CRM-129704-AA-2013-Billing-CodingGuide-3-S-ICD.pdf.
14. Centers for Medicare & Medicaid Services. Decision memo for implantable cardioverter defibrillators (ICDs) (CAG-00157N). [internet]. Baltimore (MD): Centers for Medicare & Medicaid Services (CMS), Department of Health and Human Services; 2003 Jun 6 [accessed 2012 Nov 20]. [15 p]. Available: http://www.cms.gov/medicare-coverage-database/details/nca-decision-memo.aspx?NCAId=39&fromdb=true.
15. Aetna, Inc. Clinical policy bulletin number 0585: cardioverter-defibrillators. [internet]. Hartford (CT): Aetna, Inc.; 2013 May 31 [accessed 2013 Jun 4]. [15 p]. Available: http://www.aetna.com/cpb/medical/data/500_599/0585.html.
16. Anthem Insurance Companies, Inc. Implantable cardioverter-defibrillator (ICD). [internet]. North Haven (CT): Anthem Insurance Companies, Inc.; 2013 Apr 16 [accessed 2013 Jun 4]. [16 p]. Available: http://www.anthem.com/ca/medicalpolicies/policies/mp_pw_a053321.htm.

17. BlueCross BlueShield of Arizona. Medical coverage guidelines: implantable cardioverter defibrillator, subcutaneous. Phoenix (AZ): BlueCross BlueShield of Arizona; 2012 Oct 31. 2 p. Also available: https://secure.azblue.com/pdf/medpol/o655.pdf.

18. BlueCross BlueShield of Kansas City. Implantable cardioverter defibrillator. Policy number: 7.01.44. Kansas City (MO): BlueCross BlueShield of Kansas City; 2012 Nov. 5 p. Also available: https://www.bluekc.com.

19. BlueCross BlueShield of North Carolina. Corporate medical policy: implantable cardioverter defibrillator. Durham (NC): BlueCross BlueShield of North Carolina; 2012 Oct. 5 p. Also available: https://www.bcbsnc.com/assets/services/public/pdfs/medicalpolicy/implantable_cardioverter_defibrillator.pdf.

20. CIGNA Health Corporation. CIGNA medical coverage policy: implantable cardioverter defibrillator (ICD). [internet]. Bloomfield (CT): CIGNA Health Corporation; 2013 Jan 15 [accessed 2013 Jun 4]. [21 p]. Available: http://www.cigna.com.

21. Empire Blue Cross and Blue Shield. Implantable cardioverter-defibrillator (ICD). Medical policy #SURG.00033. [internet]. New York (NY): Empire Blue Cross Blue Shield; 2013 Apr 16 [accessed 2013 Jun 4]. [20 p]. Available: http://www.empireblue.com/medicalpolicies/policies/mp_pw_a053321.htm.

22. Humana, Inc. Cardioverter defibrillators/cardiac resynchronization therapy. Medical coverage policy number: CLPD-0425-008. [internet]. Louisville (KY): Humana, Inc.; 2013 Feb 28 [accessed 2013 Jun 4]. [25 p]. Available: http://apps.humana.com/tad/tad_new/home.aspx.

23. United HealthCare Services, Inc. Omnibus codes. Policy number: 2013T0535S. Edina (MN): United HealthCare Services, Inc.; 2013 Feb 1. 62 p. Also available: https://www.unitedhealthcareonline.com/ccmcontent/ProviderII/UHC/en-US/Assets/ProviderStaticFiles/ProviderStaticFilesPdf/Tools%20and%20Resources/Policies%20and%20Protocols/Medical%20Policies/Medical%20Policies/Omnibus_Codes.pdf.

24. European Heart Rhythm Association, Heart Rhythm Society, Zipes DP, et al. ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Develop Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death). J Am Coll Cardiol. 2006 Sep 5;48(5):e247-346. PMID: 16949478

25. Expert Commenter 524. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS168 - Subcutaneous implantable cardioverter defibrillator (S-ICD System) for treatment of cardiomyopathy. 2012 Apr 10 [review date].

26. Expert Commenter 676. (PRI, Health Systems/Administration). Horizon Scanning Structured Comment Form. HS168 - Subcutaneous implantable cardioverter defibrillator (S-ICD System) for treatment of cardiomyopathy. 2012 Mar 20 [review date].

27. Expert Commenter 769. (External, Clinical). Horizon Scanning Structured Comment Form. HS168 - Subcutaneous implantable cardioverter defibrillator (S-ICD System) for treatment of cardiomyopathy. 2012 Apr 24 [review date].

28. Expert Commenter 403. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS168 - Subcutaneous implantable cardioverter defibrillator (S-ICD System) for treatment of cardiomyopathy. 2012 Apr 10 [review date].

29. Expert Commenter 1157. (External, Clinical). Horizon Scanning Structured Comment Form. HS168 - Subcutaneous implantable cardioverter defibrillator (S-ICD System) for treatment of cardiomyopathy. 2012 Mar 23 [review date].

30. Expert Commenter 397. (ECRI Institute, Applied Solutions Group). Horizon Scanning Structured Comment Form. HS168 - Subcutaneous implantable cardioverter defibrillator (S-ICD System) for treatment of cardiomyopathy. 2012 Apr 10 [review date].

31. Cardiovascular. [internet]. Carlsbad (CA): Isis Pharmaceuticals, Inc. [accessed 2011 Apr 25]. [4 p]. Available: http://www.isispharm.com/Pipeline/Therapeutic-Areas/Cardiovascular.htm.

32. Genzyme and Isis announce FDA approval of KYNAMRO (mipomersen sodium) injection for the treatment of homozygous familial hypercholesterolemia. [internet]. Cambridge (MA): Genzyme Corporation; 2013 Jan 29 [accessed 2013 Feb 21]. [10 p]. Available: http://genzyme.newshq.businesswire.com/press-release/genzyme-and-isis-announce-fda-approval-kynamro-mipomersen-sodium-injection-treatment-h.

33. FDA approves new orphan drug Kynamro to treat inherited cholesterol disorder. [internet]. Silver Spring (MD): U.S. Food and Drug Administration (FDA); 2013 Jan 29 [accessed 2013 Feb 22]. [2 p]. Available: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm337195.htm.

34. Lomitapide. [internet]. Cambridge (MA): Aegerion Pharmaceuticals, Inc. [accessed 2011 Sep 27]. [1 p]. Available: http://www.aegerion.com/programs-lomitapide.htm.

35. Aegerion Pharmaceuticals, Inc. Long term, follow-on study of lomitapide in patients with homozygous familial hypercholesterolemia. In: ClinicalTrials.gov [internet]. Bethesda (MD): National Library of Medicine (U.S.); 2000- [accessed 2012 Nov 30]. [4 p]. Available: http://www.clinicaltrials.gov/ct2/show/NCT00943306 NLM Identifier: NCT00943306.

36. Aegerion Pharmaceuticals, Inc. Aegerion Pharmaceuticals announces EMA acceptance for review of Marketing Authorization Application for lomitapide. [internet]. Cambridge (MA): Aegerion Pharmaceuticals, Inc.; 2012 Mar 20 [accessed 2012 Oct 26]. [2 p]. Available: http://ir.aegerion.com/releasedetail.cfm?ReleaseID=658286.

37. MTP-I. [internet]. Aegerion Pharmaceuticals [accessed 2011 Sep 28]. [1 p]. Available: http://www.aegerion.com/science-mtp.htm.

38. APOB. In: Genetics Home Reference [internet]. Bethesda (MD): National Library of Medicine (U.S.); 2012 Nov 25 [accessed 2012 Nov 30]. [4 p]. Available: http://ghr.nlm.nih.gov/gene/APOB.

39. Juxtapid prescribing information. Cambridge (MA): Aegerion Pharmaceuticals, Inc.; 2012 Dec. 12 p. Also available: http://www.aegerion.com/Collateral/Documents/English-US/Prescribing_Information.pdf.

40. Cuchel M, Meagher EA, du Toit Theron H, et al. Efficacy and safety of a microsomal triglyceride transfer protein inhibitor in patients with homozygous familial hypercholesterolaemia: a single-arm, open-label, phase 3 study. Lancet. 2013 Jan 5;381(9860):40-6. Epub 2012 Nov 1. PMID: 23122768

41. FDA approves Aegerion Pharmaceuticals' Juxtapid (lomitapide) capsules for homozygous familial hypercholesterolemia (HoFH). [internet]. Cambridge (MA): Aegerion Pharmaceuticals, Inc.; 2012 Dec 24 [accessed 2013 Jun 5]. [4 p]. Available: http://ir.aegerion.com/releasedetail.cfm?ReleaseID=728650.

42. Juxtapid product information. [internet]. Cambridge (MA): Aegerion Pharmaceuticals, Inc.; 2012 Dec [accessed 2013 Feb 27]. [3 p]. Available: http://www.aegerion.com/products-info.htm.

43. Aegerion Pharmaceuticals receives positive European CHMP opinion for Lojuxta (lomitapide) to treat homozygous familial hypercholesterolemia (HoFH). [internet]. Cambridge (MA): Aegerion Pharmaceuticals, Inc.; 2013 May 31 [accessed 2013 Jun 5]. [2 p]. Available: http://ir.aegerion.com/releasedetail.cfm?ReleaseID=768334.

44. Aegerion Pharmaceuticals receives European approval for Lojuxta (lomitapide) to treat homozygous familial hypercholesterolemia (HoFH). [internet]. Cambridge (MA): Aegerion Pharmaceuticals, Inc.; 2013 Aut 1 [accessed 2013 Nov 27]. [2 p]. Available: http://ir.aegerion.com/releasedetail.cfm?ReleaseID=782124.

45. Aegerion Pharmaceuticals: 3Q snapshot. New York (NY): J.P. Morgan; 2013 Oct 30. 10 p.

46. United HealthCare Services, Inc. United Healthcare pharmacy clinical pharmacy programs: Juxtapid (lomitapide). Minneapolis (MN): United HealthCare Services, Inc.; 2013 Feb. 2 p. Also available: https://www.unitedhealthcareonline.com/ccmcontent/ProviderII/UHC/en-US/Assets/ProviderStaticFiles/ProviderStaticFilesPdf/Tools%20and%20Resources/Pharmacy%20Resources/Notification_Juxtapid.pdf.

47. Humana, Inc. Juxtapid (lomitapide). Louisville (KY): Humana, Inc.; 2013 Feb 21. 6 p. Also available: http://www.humana.com.

48. Aetna, Inc. Juxtapid drug formulary search. [internet]. Hartford (CT): Aetna, Inc. [accessed 2013 Jun 5]. [2 p]. Available: https://pbm.aetna.com/wps/portal/!ut/p/c5/jY7LDoIwFES_xS-4t1oe20q0EKBaaCuwISQahchjQUjg68WdG6Mzy5MzGShgbVdN9b0a676rnpBBYZeMH9OTnxCtYooYWD5Bl5Mdcmfl-ZsbLdFzbAw8isHWGB77lCC3_7HxSxj-sC-QIS3Txh3iecyixZtUs8hZNHIRSzwLdZhHoc5Xk-g92-umCjMQft_eIIfC-ViWLsEgIjq1.

49. Juxtapid pricing info. [internet]. Santa Monica (CA): GoodRx, Inc. [accessed 2013 Nov 27]. [5 p]. Available: http://www.goodrx.com/juxtapid.

50. National Human Genome Research Institute. Learning about familial hypercholesterolemia. [internet]. Bethesda (MD): National Human Genome Research Institute, National Institutes of Health (NIH); 2011 Mar 23 [accessed 2011 Jul 12]. [3 p]. Available: http://www.genome.gov/25520184#al-4.

51. Expert Commenter 399. (ECRI Institute, Applied Solutions Group). Horizon Scanning Structured Comment Form. HS1251 - Lomitapide (Juxtapid) for treatment of homozygous familial hypercholesterolemia. 2013 Mar 15 [review date].

52. Expert Commenter 410. (ECRI Institute, Health Devices). Horizon Scanning Structured Comment Form. HS1251 - Lomitapide (Juxtapid) for treatment of homozygous familial hypercholesterolemia. 2013 Feb 18 [review date].

53. Expert Commenter 1193. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS1251 - Lomitapide (Juxtapid) for treatment of homozygous familial hypercholesterolemia. 2013 Feb 18 [review date].

54. Expert Commenter 476. (External, Clinical). Horizon Scanning Structured Comment Form. HS1251 - Lomitapide (Juxtapid) for treatment of homozygous familial hypercholesterolemia. 2013 Mar 5 [review date].

55. Expert Commenter 660. (External, Health Systems/Administration). Horizon Scanning Structured Comment Form. HS1251 - Lomitapide (Juxtapid) for treatment of homozygous familial hypercholesterolemia. 2013 Feb 18 [review date].

56. Expert Commenter 1026. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS1251 - Lomitapide (Juxtapid) for treatment of homozygous familial hypercholesterolemia. 2013 Feb 26 [review date].

57. Expert Commenter 167. (External, Clinical). Horizon Scanning Structured Comment Form. HS1147 - Standardized protocol and integrated system (RACE Project) for treatment and transfer of patients with ST-elevated myocardial infarction. 2012 Nov 7 [review date].

58. SynCardia Systems. CardioWest total artificial heart (TAH): directions for use. Tucson (AZ): SynCardia Systems, Inc.; 28 p.

59. SynCardia Systems, Inc. SynCardia freedom driver system study. In: ClinicalTrials.gov [database online]. Bethesda (MD): National Library of Medicine (U.S.); 2000- [accessed 2012 Dec 13]. [3 p]. Available: http://www.clinicaltrials.gov/ct2/show/NCT00733447 NLM Identifier: NCT00733447.

60. Clinical trials: the Freedom driver system. [internet]. Tucson (AZ): SynCardia Systems, Inc. [accessed 2012 Nov 9]. [3 p]. Available: http://www.syncardia.com/medical-professionals/clinical-trials.html.

61. Total artificial heart facts. [internet]. Tucson (AZ): SynCardia Systems, Inc. [accessed 2012 Nov 9]. [2 p]. Available: http://www.syncardia.com/total-facts/total-artificial-heart-facts.html.

62. Reliability second to none. [internet]. Tucson (AZ): SynCardia Systems, Inc. [accessed 2012 Nov 9]. [1 p]. Available: http://www.syncardia.com/Medical-Professionals/reliability-second-to-none.html.

63. Friedline K, Hassinger P. Total artificial heart Freedom driver in a patient with end-stage biventricular heart failure. AANA J. 2012 Apr;80(2):105-12. Also available: https://www.aanadc.com/newsandjournal/Documents/totalheart-0412-p105-112.pdf. PMID: 22586879

64. Former semi-pro arena football player bridged to heart transplant with the SynCardia Total Artificial Heart. [internet]. Tucson (AZ): SynCardia Systems, Inc.; 2013 May 30 [accessed 2013 Jun 11]. [3 p]. Available: http://www.syncardia.com/2013-press-releases/former-semi-pro-arena-football-player-bridged-to-heart-transplant-with-the-syncardia-total-artificial-heart.html.

65. Intermountain Medical Center uses SynCardia total artificial heart to bridge 31-year-old father to a heart transplant. [internet]. Tucson (AZ): SynCardia Systems, Inc.; 2013 Mar 21 [accessed 2013 Jun 11]. [2 p]. Available: http://www.syncardia.com/2013-press-releases/intermountain-medical-center-uses-syncardia-total-artificial-heart-to-bridge-31-year-old-father-to-a-heart-transplant.html.

66. 74-year-old becomes oldest total artificial heart patient to leave hospital using the Freedom portable driver. [internet]. Tucson (AZ): SynCardia Systems, Inc.; 2013 Jan 15 [accessed 2013 Jun 11]. [2 p]. Available: http://www.syncardia.com/2013-press-releases/74-year-old-becomes-oldest-syncardia-total-artificial-heart-patient-to-leave-the-hospital-using-the-freedom-portable-driver.html.

67. Home for the holidays: 1st SynCardia Total Artificial Heart patient discharged from UCLA. [internet]. Tucson (AZ): SynCardia Systems, Inc.; 2013 Jan 10 [accessed 2013 Jun 11]. [2 p]. Available: http://www.syncardia.com/2013-press-releases/home-for-the-holidays-1st-syncardia-total-artificial-heart-patient-discharged-from-ucla.html.

68. French man with SynCardia total artificial heart surpasses two years of support. [internet]. Tucson (AZ): SynCardia Systems, Inc.; 2013 Aug 15 [accessed 2013 Nov 27]. [2 p]. Available: http://www.syncardia.com/2013-press-releases/french-man-with-syncardia-total-artificial-heart-surpasses-two-years-of-support/itemid-1337.html.

69. 510(k) summary of safety and effectiveness data. CardioWest temporary total artificial heart. Rockville (MD): U.S. Food and Drug Administration (FDA); 2004 Oct 15. 28 p. Also available: http://www.fda.gov.

70. Freedom driver system receives CE mark to power SynCardia's total artificial heart in Europe. [internet]. Tucson (AZ): SynCardia Systems, Inc.; 2010 Mar 4 [accessed 2010 Mar 4]. [1 p]. Available: http://www.syncardia.com/2010-Press-Release/freedom-driver-system-receives-ce-mark-to-power-syncardias-total-artificial-heart-in-europe.html.

71. 1,200th worldwide implant of the SynCardia total artificial heart occurs in Indiana. [internet]. Tucson (AZ): SynCardia Systems, Inc.; 2013 Nov 5 [accessed 2013 Dec 6]. [3 p]. Available: http://www.syncardia.com/2013-press-releases/1200th-worldwide-implant-of-the-syncardia-total-artificial-heart-occurs-in-indiana/itemid-1337.html.

72. ECRI Institute. Total artificial heart as bridge to transplantation and destination therapy. Plymouth Meeting (PA): ECRI Institute; 2009 Oct. 16 p. (Emerging Technology Evidence Report).

73. PricePaid [database online]. Plymouth Meeting (PA): ECRI Institute [accessed 2012 Dec 13]. PricePaid search summary: device: prostheses, heart, transcutaneously powered. [1 p]. Available: http://www.ecri.org.

74. Jessup M, Abraham WT, Casey DE, et al. 2009 focused update: ACCF/AHA guidelines for the diagnosis and management of heart failure in adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2009 Apr 14;119(14):1977-2016. PMID: 19324967

75. Expert Commenter 396. (ECRI Institute, Applied Solutions Group). Horizon Scanning Structured Comment Form. HS334 - CardioWest total artificial heart with portable Freedom driver system as bridge to heart transplantation. 2012 Apr 13 [review date].

76. Expert Commenter 167. (External, Clinical). Horizon Scanning Structured Comment Form. HS334 - CardioWest total artificial heart with portable Freedom driver system as bridge to heart transplantation. 2012 Apr 18 [review date].

77. Expert Commenter 41. (External, Clinical). Horizon Scanning Structured Comment Form. HS334 - CardioWest total artificial heart with portable Freedom driver system as bridge to heart transplantation. 2012 Apr 19 [review date].

78. Expert Commenter 1011. (External, Health Systems/Administration). Horizon Scanning Structured Comment Form. HS334 - CardioWest total artificial heart with portable Freedom driver system as bridge to heart transplantation. 2012 Apr 18 [review date].

79. Expert Commenter 421. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS334 - CardioWest total artificial heart with portable Freedom driver system as bridge to heart transplantation. 2012 Apr 10 [review date].

80. Expert Commenter 403. (ECRI Institute, Health Devices). Horizon Scanning Structured Comment Form. HS334 - CardioWest total artificial heart with portable Freedom driver system as bridge to heart transplantation. 2012 Apr 10 [review date].

81. Expert Commenter 424. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS334 - CardioWest total artificial heart with portable Freedom driver system as bridge to heart transplantation. 2012 Apr 10 [review date].

82. National Heart, Lung, and Blood Institute (NHLBI). Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report [NIH Publication No. 04-5230]. Washington (DC): National Heart, Lung, and Blood Institute (NHLBI), National Institutes of Health (NIH); 2004 Aug. 87 p. Also available: http://www.nhlbi.nih.gov/guidelines/hypertension/jnc7full.pdf.

83. Bisognano JD, Bakris G, Nadim MK, et al. Baroreflex activation therapy lowers blood pressure in patients with resistant hypertension: results from the double-blind, randomized, placebo-controlled Rheos pivotal trial. J Am Coll Cardiol. 2011 Aug 9;58(7):765-73. PMID: 21816315

84. Chobanian AV, Bakris GL, Black HR, et al. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension. 2003 Dec;42(6):1206-52. PMID: 14656957

85. Nielsen PE, Bell G, Augustenborg G, et al. Reduction in distal blood pressure by sympathetic nerve block in patients with occlusive arterial disease. Cardiovasc Res. 1973 Sep;7(5):577-84. PMID: 4753292

86. Thulesius O, Gjores JE, Mandaus L. Distal blood flow and blood pressure in vascular occlusion; influence of sympathetic nerves on collateral blood flow. Scand J Clin Lab Invest Suppl. 1973;128:53-7. PMID: 4764598

87. Esler MD, Krum H, Sobotka PA, et al. Renal sympathetic denervation in patients with treatment-resistant hypertension (the Symplicity HTN-2 trial): a randomised controlled trial. Lancet. 2010 Dec 4-10;376(9756):1903-9.

88. Gewirtz JR, Bisognano JD. Catheter-based renal sympathetic denervation: a targeted approach to resistant hypertension. Cardiol J. 2011;18(1):97-102. PMID: 21305496

89. About the procedure. [internet]. Minneapolis (MN): Medtronic, Inc. [accessed 2012 Nov 14]. [2 p]. Available: http://www.medtronicrdn.com/intl/healthcare-professionals/about-rdn/about-the-procedure/index.htm.

90. Medtronic starts landmark study of hypertension treatment. U.S. clinical trial of Symplicity Renal Denervation System enrolls first patient. [internet]. Minneapolis (MN): Medtronic, Inc.; 2011 Oct 26 [accessed 2012 Mar 6]. [3 p]. Available: http://newsroom.medtronic.com/phoenix.zhtml?c=251324&p=irol-newsArticle&ID=1772994&highlight=.

91. The Symplicity catheter system. [internet]. Mountain View (CA): Medtronic, Inc. [accessed 2011 Jul 22]. [1 p]. Available: http://www.ardian.com/ous/medical-professionals/system.shtml [Internet Archive access date 2013 Dec 2] Available: http://web.archive.org/web/20110807175512/http://www.ardian.com/ous/medical-professionals/system.shtml].

92. The Symplicity renal denervation system. [internet]. Minneapolis (MN): Medtronic, Inc. [accessed 2012 Nov 14]. [2 p]. Available: http://www.medtronicrdn.com/intl/healthcare-professionals/symplicity-rdn-system/index.htm.

93. Symplicity overview. [internet]. Minneapolis (MN): Medtronic, Inc. [accessed 2012 Mar 7]. [1 p]. Available: Available: http://www.ardian.com/ous/patients/symplicity.shtml [Internet Archive access date 2013 Dec 2] Available: http://web.archive.org/web/20120905131518/http://www.ardian.com/ous/medical-professionals/system.shtml.

94. Cohen DL, Townsend RR. Renal denervation revisited: promising treatment for resistant hypertension? J Clin Hypertens (Greenwich). 2011 Dec;13(12):931-2.

95. Medtronic, Inc. New data reinforce significant blood pressure reduction sustained to two years using the Symplicity renal denervation system. [internet]. Minneapolis (MN): Medtronic, Inc.; 2013 Mar 10 [accessed 2013 Jun 10]. [2 p]. Available: http://newsroom.medtronic.com/phoenix.zhtml?c=251324&p=irol-newsArticle&ID=1802677&highlight=symplicity.

96. Medtronic, Inc. Medtronic announces data from largest real-world patient population confirm strong safety profile and clinical efficacy of renal denervation with the Symplicity system. [internet]. Minneapolis (MN): Medtronic, Inc.; 2013 May 21 [accessed 2013 Jun 10]. [3 p]. Available: http://investorrelations.medtronic.com/phoenix.zhtml?c=76126&p=irol-newsArticle&id=1822481.

97. Geisler BP, Egan BM, Cohen JT, et al. Cost-effectiveness and clinical effectiveness of catheter-based renal denervation for resistant hypertension. J Am Coll Cardiol. 2012 Oct 2;60(14):1271-7. Epub 2012 Sep 12. PMID: 22981547

98. Medtronic completes acquisition of Ardian. [internet]. Mountain View (CA): Medtronic, Inc.; 2011 Jan 13 [accessed 2011 Jul 22]. [3 p]. Available: http://newsroom.medtronic.com/phoenix.zhtml?c=251324&p=irol-newsArticle&ID=1770617&highlight=.

99. St. Jude Medical announces European approval and launch of the EnligHTN renal. [internet]. St. Paul (MN): St. Jude Medical, Inc.; 2012 May 15 [accessed 2013 Feb 26]. [2 p]. Available: http://www.sjm.com/corporate/media-room/media-kits/new-products/~/media/SJM/corporate/Media%20Kits/Updated%20PDFs/51512%20RD%20Launch%20Press%20Release%20FINAL%20ver%202.ashx.

100. Boston Scientific Corporation. New data demonstrate significant and sustained blood pressure reduction with Boston Scientific Vessix renal denervation system. [internet]. Natick (MA): Boston Scientific Corporation; 2013 May 22 [accessed 2013 Jun 10]. [3 p]. Available: http://bostonscientific.mediaroom.com/2013-05-22-New-Data-Demonstrate-Significant-And-Sustained-Blood-Pressure-Reduction-With-Boston-Scientific-Vessix-Renal-Denervation-System.

101. Medtronic, Inc. Medtronic completes enrollment in landmark U.S. study of Simplicity renal denervation system for treatment-resistant hypertension. [internet]. Minneapolis (MN): Medtronic, Inc.; 2013 May 23 [accessed 2013 Jun 10]. [2 p]. Available: http://investorrelations.medtronic.com/phoenix.zhtml?c=76126&p=irol-newsArticle_print&ID=1823681&highlight.

102. Medtronic Vascular. Renal denervation in patients with uncontrolled hypertension (SYMPLICITY HTN-3). In: Clinicaltrials.gov [database online]. Bethesda (MD): National Library of Medicine (U.S.); 2000- [accessed 2012 Nov 9]. [3 p]. Available: http://clinicaltrials.gov/ct2/show/NCT01418261 NLM Identifier: NCT01418261.

103. Expert Commenter 596. (External, Clinical). Horizon Scanning Structured Comment Form. HS613 - Radiofrequency ablation (Symplicity System) for renal denervation for treatment-resistant hypertension. 2012 Apr 24 [review date].

104. Expert Commenter 676. (PRI, Health Systems/Administration). Horizon Scanning Structured Comment Form. HS613 - Radiofrequency ablation (Symplicity System) for renal denervation for treatment-resistant hypertension. 2012 Apr 18 [review date].

105. Expert Commenter 394. (ECRI Institute, Applied Solutions Group). Horizon Scanning Structured Comment Form. HS613 - Radiofrequency ablation (Symplicity System) for renal denervation for treatment-resistant hypertension. 2012 Apr 19 [review date].

106. Expert Commenter 409. (ECRI Institute, Health Devices). Horizon Scanning Structured Comment Form. HS613 - Radiofrequency ablation (Symplicity System) for renal denervation for treatment-resistant hypertension. 2012 Apr 20 [review date].

107. Expert Commenter 480. (External, Clinical). Horizon Scanning Structured Comment Form. HS613 - Radiofrequency ablation (Symplicity System) for renal denervation for treatment-resistant hypertension. 2012 Apr 23 [review date].

108. Expert Commenter 423. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS613 - Radiofrequency ablation (Symplicity System) for renal denervation for treatment-resistant hypertension. 2012 Apr 19 [review date].

109. Ren X. Aortic stenosis treatment & management. In: Medscape Reference [internet]. New York (NY): WebMD, LLC [accessed 2012 Nov 12]. [10 p]. Available: http://emedicine.medscape.com/article/150638-treatment.

110. Medtronic, Inc. Severe aortic stenosis treatment options. [internet]. Minneapolis (MN): Medtronic, Inc. [accessed 2012 Nov 14]. [2 p]. Available: http://www.medtronic.com/.

111. Treatment options for heart valve disease: open chest heart valve surgery. In: YourHeartValve.com [internet]. Irvine (CA): Edwards Lifesciences LLC [accessed 2012 Nov 12]. [2 p]. Available: http://www.yourheartvalve.com/treatmentoptions/Pages/openchestsurgery.aspx.

112. Treatment options for heart valve disease: the transcatheter approach (TAVR). In: YourHeartValve.com [internet]. Irvine (CA): Edwards Lifesciences LLC [accessed 2012 Nov 12]. [11 p]. Available: http://www.yourheartvalve.com/treatmentoptions/Pages/transcatheterapproach.aspx.

113. Dichtl W, Alber HF, Feuchtner GM, et al. Prognosis and risk factors in patients with asymptomatic aortic stenosis and their modulation by atorvastatin (20 mg). Am J Cardiol. 2008 Sep 15;102(6):743-8. PMID: 18774000

114. Prostacyclin. [internet]. San Francisco (CA): PHCentral [accessed 2011 Sep 20]. [2 p]. Available: http://www.phcentral.org/medical/treatments/prostacyclin.

115. Pilgrim T, Wenaweser P, Meuli F, et al. Clinical outcome of high-risk patients with severe aortic stenosis and reduced left ventricular ejection fraction undergoing medical treatment or TAVI. PLoS ONE. 2011;6(11):e27556. PMID: 22102909

116. Bande M, Michev I, Sharp AS, et al. Percutaneous transcatheter aortic valve implantation: past accomplishments, present achievements and applications, future perspectives. Cardiol Rev. 2010 May-Jun;18(3):111-24. PMID: 20395696

117. Dworakowski R, MacCarthy PA, Monaghan M, et al. Transcatheter aortic valve implantation for severe aortic stenosis-a new paradigm for multidisciplinary intervention: a prospective cohort study. Am Heart J. 2010 Aug;160(2):237-43. PMID: 20691827

118. Sambu N, Curzen N. Transcatheter aortic valve implantation: the state of play. Future Cardiol. 2010 Mar;6(2):243-54. PMID: 20230265

119. CoreValve system. [internet]. Minneapolis (MN): Medtronic, Inc. [accessed 2011 Sep 22]. [2 p]. Available: http://www.medtronic.com/.

120. Medtronic CoreValve system. Minneapolis (MN): Medtronic, Inc.; 2011. 1 p.

121. Corevalve evolut - TruFit technology. [internet]. Minneapolis (MN): Medtronic, Inc. [accessed 2013 Apr 19]. [3 p]. Available: http://www.corevalveevolut.com/root/corevalve-evolut/trufit-technology/index.htm.

122. CoreValve transcatheter aortic valve implantation. Minneapolis (MN): Medtronic, Inc.; 2011. 15 p.

123. Holzinger C, Podesser BK, Haumberger W, et al. Transcatheter aortic valve implantation - TAVI: early results from the transapical approach in a multimorbid, elderly, high-risk population. Eur Surg. 2011 Apr;43(2):99-102.

124. Walther T, Mollmann H, van Linden A, et al. Transcatheter aortic valve implantation transapical: step by step. Semin Thorac Cardiovasc Surg. 2011;23(1):55-61. PMID: 21807300

125. Medtronic CoreValve System gains CE mark for new direct aortic approach to transcatheter aortic valve implantation. [internet]. Minneapolis (MN): Medtronic, Inc.; 2011 Nov 7 [accessed 2011 Nov 10]. [2 p]. Available: http://wwwp.medtronic.com/Newsroom/NewsReleaseDetails.do?itemId=1320264670364&lang=en_US.

126. Etienne PY, Papadatos S, El Khoury E, et al. Transaortic transcatheter aortic valve implantation with the Edwards SAPIEN valve: feasibility, technical considerations, and clinical advantages. Ann Thorac Surg. 2011 Aug;92(2):746-8. PMID: 21801942

127. Medtronic CoreValve ADVANCE study demonstrates low rates of mortality and stroke and sustained valve performance. [internet]. Minneapolis (MN): Medtronic, Inc.; 2013 May 21 [accessed 2013 Jun 12]. [1 p]. Available: http://newsroom.medtronic.com/phoenix.zhtml?c=251324&p=irol-newsArticle&ID=1822489&highlight=corevalve.

128. CoreValve data cause FDA to waive panel requirement. [internet]. EP Vantage; 2013 Oct 30 [accessed 2013 Nov 27]. [2 p]. Available: http://www.epvantage.com/Universal/View.aspx?type=WordSearch&query=CoreValve&dr=3&epo=true&sb=date&so=descending#&&_ViewArgs=%7b%22_EntityType%22%3a0%2c%22_Parameters%22%3a%7b%22_ContextData%22%3a%22%7b%5c%22isEPVantage%5c%22%3atrue%2c%5c%22percentag.

129. Medtronic, Inc. Medtronic gains CE mark for CoreValve Evolut 23mm. [internet]. Minneapolis (MN): Medtronic, Inc.; 2012 Sep 26 [accessed 2012 Nov 14]. [1 p]. Available: http://wwwp.medtronic.com/Newsroom/NewsReleaseDetails.do?itemId=1348597971971&lang=en_US.

130. Medtronic Vascular. Safety and efficacy study of the Medtronic CoreValve system in the treatment of symptomatic severe aortic stenosis in high risk and very high risk subjects who need aortic valve replacement. In: ClinicalTrials.gov [database online]. Bethesda (MD): National Library of Medicine (U.S.); 2000- [accessed 2011 Sep 22]. [5 p]. Available: http://clinicaltrials.gov/ct2/show/NCT01240902 NLM Identifier: NCT01240902.

131. Centers for Medicare & Medicaid Services (CMS). Decision memo for transcatheter aortic valve replacement (TAVR) (CAG-00430N). Baltimore (MD): Centers for Medicare & Medicaid Services (CMS); 2012. 41 p. Also available: http://www.cms.gov/medicare-coverage-database/shared/handlers/highwire.ashx?url=http://www.cms.gov/medicare-coverage-database/details/nca-decision-memo.aspx@@@NCAId$$$257&session=w12fth45id1pbf55dnui3j2m&kq=1718690667.

132. Aetna, Inc. Clinical policy bulletin: transcatheter aortic valve implantation. Number: 0826. [internet]. Hartford (CT): Aetna, Inc.; 2012 Dec 21 [accessed 2013 Apr 26]. [12 p]. Available: http://www.aetna.com/cpb/medical/data/800_899/0826.html.

133. United HealthCare Services, Inc. Transcatheter heart valve procedures. Policy number: 2013T0557B. Edina (MN): United HealthCare Services, Inc.; 2013 Jan 1. 14 p. Also available: https://www.unitedhealthcareonline.com.

134. Medica. Medica coverage policy: transcatheter heart valve replacement and repair procedures. [internet]. Minnetonka (MN): Medica; 2013 Feb 1 [accessed 2013 Apr 26]. [3 p]. Available: http://provider.medica.com.

135. Blue Cross Blue Shield of Massachusetts. Transcatheter aortic-valve implantation for aortic stenosis. Policy #392. [internet]. Boston (MA): Blue Cross Blue Shield of Massachusetts; 2012 Nov 1 [accessed 2013 Apr 26]. [4 p]. Available: https://www.bcbsma.com.

136. Humana, Inc. Transcatheter valve implantation. Medical coverage policy number: CLPD-0508-001. Louisville (KY): Humana, Inc.; 2013 Jan 24. 18 p. Also available: http://apps.humana.com/tad/tad_new/home.aspx.

137. Wellmark, Inc. Transcatheter pulmonary valve implantation. Medical policy: 02.02.15. [internet]. Des Moines (IA): Wellmark, Inc.; 2012 Jul [accessed 2012 Jul 30]. [3 p]. Available: http://www.wellmark.com/.

138. American College of Cardiology, American Heart Association Task Force on Practice Guidelines (Writing Committee, Society of Cardiovascular Anesthesiologists), Bonow RO, et al.ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (writing Committee to Revise the 1998 guidelines for the management of patients with valvular heart disease) developed in collaboration with the Society of Cardiovascular Anesthesiologists endorsed by the Society for Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons. J Am Coll Cardiol. 2006 Aug 1;48(3):e1-148. PMID: 16875962

139. Treatment options for heart valve disease: medications. In: YourHeartValve.com [internet]. Irvine (CA): Edwards Lifesciences LLC [accessed 2012 Nov 12]. [1 p]. Available: http://www.yourheartvalve.com/treatmentoptions/Pages/medication.aspx.

140. U.S. Food and Drug Administration (FDA). Edwards SAPIEN transcatheter heart valve (THV) - P110021. [internet]. Silver Spring (MD): U.S. Food and Drug Administration (FDA) [accessed 2012 Nov 14]. [2 p]. Available: http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/Recently-ApprovedDevices/ucm327342.htm.

141. Medtronic Cardiovascular. Safety and efficacy continued access study of the Medtronic CoreValve system in the treatment of symptomatic severe aortic stenosis in very high risk subjects and high risk subjects who need aortic valve replacement. In: ClinicalTrials.gov [database online]. Bethesda (MD): National Library of Medicine (U.S.); 2000- [accessed 2012 Nov 14]. [4 p]. Available: http://www.clinicaltrials.gov/ct2/show/NCT01531374 NLM Identifier: NCT01531374.

142. Medtronic Cardiovascular. Safety and efficacy study of the Medtronic CoreValve system in the treatment of severe, symptomatic aortic stenosis in intermediate risk subjects who need aortic valve replacement (SURTAVI). In: ClinicalTrials.gov [database online]. Bethesda (MD): National Library of Medicine (U.S.); 2000- [accessed 2012 Nov 14]. [5 p]. Available: http://www.clinicaltrials.gov/ct2/show/NCT01586910 NLM Identifier: NCT01586910.

143. Expert Commenter 396. (ECRI Institute, Applied Solutions Group). Horizon Scanning Structured Comment Form. HS914 - Transcatheter aortic valve (CoreValve) implantation for treatment of severe aortic stenosis. 2012 Apr 13 [review date].

144. Expert Commenter 41. (External, Clinical). Horizon Scanning Structured Comment Form. HS914 - Transcatheter aortic valve (CoreValve) implantation for treatment of severe aortic stenosis. 2012 Apr 23 [review date].

145. Expert Commenter 524. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS914 - Transcatheter aortic valve (CoreValve) implantation for treatment of severe aortic stenosis. 2012 Apr 13 [review date].

146. Expert Commenter 676. (PRI, Health Systems/Administration). Horizon Scanning Structured Comment Form. HS914 - Transcatheter aortic valve (CoreValve) implantation for treatment of severe aortic stenosis. 2012 Apr 5 [review date].

147. Expert Commenter 278. (External, Clinical). Horizon Scanning Structured Comment Form. HS914 - Transcatheter aortic valve (CoreValve) implantation for treatment of severe aortic stenosis. 2012 Apr 23 [review date].

148. Expert Commenter 1174. (ECRI Institute, Health Devices). Horizon Scanning Structured Comment Form. HS914 - Transcatheter aortic valve (CoreValve) implantation for treatment of severe aortic stenosis. 2012 Apr 10 [review date].

149. Expert Commenter 423. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS914 - Transcatheter aortic valve (CoreValve) implantation for treatment of severe aortic stenosis. 2012 Apr 13 [review date].

150. Whitlow PL, Feldman T, Pedersen WR, et al. Acute and 12-month results with catheter-based mitral valve leaflet repair: the EVEREST II (endovascular valve edge-to-edge repair) high risk study. J Am Coll Cardiol. 2012 Jan 10;59(2):130-9. PMID: 22222076

151. Jilaihawi H, Hussaini A, Kar S. MitraClip: a novel percutaneous approach to mitral valve repair. J Zhejiang Univ Sci B. 2011 Aug;12(8):633-7. PMID: 21796803

152. Mayo Clinic staff. Mitral valve regurgitation. Rochester (MN): Mayo Foundation for Medical Education and Research (MFMER); 2009 Sep 18. 11 p. Also available: http://www.mayoclinic.com/health/mitral-valve-regurgitation/DS00421.

153. Vahanian A, Iung B. 'Edge to edge' percutaneous mitral valve repair in mitral regurgitation: it can be done but should it be done? Eur Heart J. 2010 Jun;31(11):1301-4. PMID: 20385570

154. Data from landmark clinical trial of Abbott's MitraClip system demonstrate durable clinical benefits for patients with mitral regurgitation two years after treatment. [internet]. New Orleans (LA): Abbott; 2011 Apr 4 [accessed 2011 Nov 14]. [3 p]. Available: http://www.abbott.com/news-media/press-releases/2011Apr04.htm.

155. Feldman T, Kar S, Rinaldi M, et al. Percutaneous mitral repair with the MitraClip system: safety and midterm durability in the initial EVEREST (Endovascular Valve Edge-to-Edge REpair Study) cohort. J Am Coll Cardiol. 2009 Aug 18;54(8):686-94. PMID: 19679246

156. MitraClip mitral valve repair system. [internet]. Abbott Park (IL): Abbott Vascular [accessed 2011 Nov 14]. [2 p]. Available: http://www.abbottvascular.com/int/mitraclip.html.

157. Pleger ST, Schulz-Schonhagen M, Geis N, et al. One year clinical efficacy and reverse cardiac remodelling in patients with severe mitral regurgitation and reduced ejection fraction after MitraClip implantation. Eur J Heart Fail. 2013 Aug;15(8):919-27. PMID: 23512096

158. Grasso C, Capodanno D, Scandura S, et al. One- and twelve-month safety and efficacy outcomes of patients undergoing edge-to-edge percutaneous mitral valve repair (from the GRASP Registry). Am J Cardiol. 2013 May 15;111(10):1482-7. Epub 2013 Feb 20. PMID: 23433761

159. U.S. Food and Drug Administration (FDA). MitraClip Clip Delivery System - P100009. [internet]. Rockville (MD): U.S. Food and Drug Administration (FDA); 2013 Nov 15 [accessed 2013 Nov 27]. [2 p]. Available: http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/Recently-ApprovedDevices/ucm375149.htm.

160. U.S. Food and Drug Administration (FDA). Brief summary of the Circulatory System Devices Panel meeting. Rockville (MD): U.S. Food and Drug Administration (FDA); 2013 Mar 20. 3 p. Also available: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/CirculatorySystemDevicesPanel/UCM345235.pdf.

161. Medical device alert: mitral valve repair system, MitraClip clip delivery system manufactured by Abbott Vascular. [internet]. London (UK): Medicines and Healthcare products Regulatory Agency (MHRA); 2013 Mar 19 [accessed 2013 Apr 19]. [5 p]. Available: http://www.mhra.gov.uk/home/groups/dts-bs/documents/medicaldevicealert/con251945.pdf.

162. Abbott recall followed by FDA request for more Mitraclip data. Devices Diagn Lett 2011 Jul 25;38(29).

163. United HealthCare Services, Inc. Transcatheter heart valve procedures. Policy number: 2013T0557C. Edina (MN): United HealthCare Services, Inc.; 2013 Apr 1. 13 p. Also available: https://www.unitedhealthcareonline.com/ccmcontent/ProviderII/UHC/en-US/Assets/ProviderStaticFiles/ProviderStaticFilesPdf/Tools%20and%20Resources/Policies%20and%20Protocols/Medical%20Policies/Medical%20Policies/Transcatheter_Heart_Valve_Procedures.pdf.

164. Expert Commenter 278. (External, Clinical). Horizon Scanning Structured Comment Form. HS330 - Transcatheter mitral valve repair (MitraClip) for treatment of mitral regurgitation. 2012 Sep 10 [review date].

165. Expert Commenter 395. (ECRI Institute, Applied Solutions Group). Horizon Scanning Structured Comment Form. HS330 - Transcatheter mitral valve repair (MitraClip) for treatment of mitral regurgitation. 2012 Sep 13 [review date].

166. Expert Commenter 403. (ECRI Institute, Health Devices). Horizon Scanning Structured Comment Form. HS330 - Transcatheter mitral valve repair (MitraClip) for treatment of mitral regurgitation. 2012 Sep 17 [review date].

167. Expert Commenter 423. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS330 - Transcatheter mitral valve repair (MitraClip) for treatment of mitral regurgitation. 2012 Sep 18 [review date].

168. Expert Commenter 433. (External, Health Systems/Administration). Horizon Scanning Structured Comment Form. HS330 - Transcatheter mitral valve repair (MitraClip) for treatment of mitral regurgitation. 2012 Oct 10 [review date].

169. Expert Commenter 1193. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS330 - Transcatheter mitral valve repair (MitraClip) for treatment of mitral regurgitation. 2012 Sep 17 [review date].

170. Expert Commenter 1195. (External, Research/Scientific/Technical). Horizon Scanning Structured Comment Form. HS330 - Transcatheter mitral valve repair (MitraClip) for treatment of mitral regurgitation. 2012 Sep 18 [review date].